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ROUND TABLE DISCUSSIONS

Fiftieth Anniversary of the Medical School

University of Minnesota

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Fiftieth Anniversary

of the

Medical School

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University of Minnesota

ROUND TABLE

October 12, 1939

THE fiftieth anniversary of the founding of the medical school of the University was the occasion of a scientific program held October 12, 13 and 14, 1939, at the University. The theme of the three-day meeting was: Some Trends in Medical Progress with Particular Reference to Chemistry in Medicine.

The main address delivered during the three-day session will be published in the near future by the University of Minnesota press. The Round Table discussions, held October 12 and 13, were considered of sufficient interest to warrant publication and are here presented in the form of a supplement to the January, 1940, issue of MINNESOTA MEDICINE.

With the discussions appear brief bibliographic sketches of the leaders in the various Round Table groups.

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Volume 23 JANUARY, 1940 No. 1

THE CLINICAL SIGNIFICANCE OF WATER AND ELECTROLYTE BALANCES

Chairman: DR. ANCEL KEYS
Professor of Physiology
University of Minnesota

Leader: DR. JOHN P. PETERS
Professor of Medicine
Yale University

DR. A. KEYS: The subject matter of this Round Table has its general interest distributed over a wide range of subjects from physics to the application in the clinic, and I think this is reflected in the large number of people in attendance today. That makes a limitation, of course, on the freedom of discussion and the intimacy of the conversations which we associate with the idea of the Round Table.

I think all of you were interested this morning to hear Dr. Peters bringing his emphasis to bear on the question as to the freedom of movement, of electrolytes and of water, within the body and within the different organs of the body. Sixteen years ago the classic paper of Van Slyke, Wu and McLean initiated what we thought was a final solution to the problem of distribution of the electrolytes in terms of Donnan equilibrium. Many of these ideas originated from the work of Dr. Peters and his collaborators. The Donnan approach supplied the first approximation, and now that we see that the system is more complicated we need a second approximation.

The interest and research in this general question of mineral and water metabolism began with the osmotic studies of the middle of the last century. We have seen the field grow, the emphasis being placed for a time on the specific physiological properties of the different mineral electrolytes and the concept of antagonism. We saw then the minerals drawn into the field of the acid base balance, particularly in the interrelations with the buffer systems in the blood. A great many researches of a brilliant character were carried out along those lines. In recent years there has been a growing interest in the relation between the electrolytes and the hormones, notably the adrenal cortex and secondarily the hormones of the pancreas, the adrenal medulla and the other endocrine organs. A new field has developed which is concerned with the interrelation between the electrolytes and the metabolism of organic substances, particularly the carbohydrates. We see now that when we discuss the mineral ions we must take into account not merely the physical properties of membranes but also the questions of electrolyte-organic combinations and the influence of the endocrine glands and their secretions on these combinations.

Dr. Peters will initiate the discussion now with some informal remarks on the general subject.

DR. JOHN P. PETERS, John Slade Ely Professor of Medicine at Yale University, has for many years combined with the practice and teaching of the healing art at the bedside, a thorough laboratory study of chemistry as applied to the diagnosis and treatment of disease.

With Dr. Donald D. Van Slyke of the Hospital of the Rockefeller Institute in New York City, he is the author of authoritative and widely read books on this aspect of science in medicine. Dr. Peters' investigations have dealt for the most part with the chemistry underlying the movement of fluids and dissolved substances within the body, a problem which medical men consider of consequence in many diseases but which have their most obvious application in diseases of the heart and kidneys. A scholarly consideration of these and related subjects has been presented by Dr. Peters in numerous publications and in a book which he has entitled simply "Body Water."

Dr. Peters is a native of Philadelphia and received his earlier training at Yale and Columbia Universities.

DR. JOHN PETERS: The title of this conference, "The Clinical Significance of Water and Electrolyte Balances," seems to me to embody a most invidious concept. It carries the implication that clinical medicine is not part of the physiological sciences but that it merely impinges upon it.

I should like to enlarge somewhat on the subject on which I opened this morning, the necessity of forsaking the categorical method in the consideration of physiological problems. Specialization in technical procedures is essential to expert work, but when specialization is allowed to carry over into the philosophical domain, it becomes a vicious bar to progress. Water and electrolyte balances are not independent functions. They do not exist for and of themselves; hence they are merely expressions of metabolic processes. Their measurement must, therefore, be ultimately purposeless unless this fundamental relationship is kept continuously in mind, and I believe it has not been. In the work of the last ten years certain general hypotheses have been established. The Starling hypothesis concerns the movement of fluids and diffusible solutes to and from the blood vessels; it states that such movements are governed by the interplay of the opposing forces of capillary blood pressure, and colloid osmotic pressure.

The Starling concept is a recognized part of clinical physiology that has worked a beneficent revolution in clinical practice. There are few left to deny that the kidneys perform their function by withdrawing solutes and water and adding certain solutes to a glomerular ultrafiltrate, the formation of which is governed by the Starling principle. However, in this connection physiologists and clinicians have been slow in escaping from their old habit patterns of regarding the kidneys as purely excretory organs resembling somewhat complicated sieves.

The universal equality of osmotic pressure throughout cells and fluids of the body is quite generally accepted, as is the fact that all cells are bathed in an undifferentiated fluid, which has the characteristics of an ultrafiltrate of serum. Likewise it has been reasonably well established that sodium and chloride are, with few exceptions, excluded from the cells of the body and are confined to this interstitial fluid. It follows from these two facts that, other things being equal, the water content of the cells of the body is determined by the concentration of sodium in the interstitial fluid.

The obvious clinical inference is that conditions which lead to sodium depletion must cause the cells of the body to imbibe water, thus diluting their contents and consequently disorganizing the chemical processes within them. The growing recognition of the necessity of maintaining the concentration of sodium and chloride in the body at optimum levels has greatly improved the treatment of post-operative states, vomiting, diabetes, advanced nephritis, and a variety of other conditions in which dehydration and salt depletion develop for one reason or another. Because the distribution of water and the hydration of cells varies with the sodium concentration of the serum it has been inferred that the osmotic effect of this sodium must be balanced within the cells by an osmotically equal load of potassium. This is not, however, an inevitable corollary; interstitial fluid is a relatively simple medium in which inorganic ions are almost unrestrained.

The contents of the cells are highly complex and all that we have learned of them would lead us to suppose that the activities of even their inorganic constituents are highly conditioned. This difference is evidenced by the extraordinary tolerance of the organism to extreme changes in concentration and quantities of sodium and chloride. All the disturbance produced by such alterations can be attributed apparently to their effects on osmotic or acid-base equilibrium. In other respects, sodium and chloride appear to be physiologically almost inert. They have little or no influence upon metabolic processes from which they are excluded by the cellular membrane. Potassium and magnesium, on the other hand, play important and essential roles. Their injection is followed by toxic symptoms quite unrelated to and out of proportion to their possible effects on osmotic pressure and acid-base equilibrium. These symptoms are presumably evidences of disturbances of the metabolic processes in which these elements participate within the cells.

Exogenous potassium salts are excreted almost like foreign bodies with more economy of water than is exercised in the excretion of exogenous sodium salts. There is something logical then in the conventional association of wa-

ter with sodium and chloride. But if knowledge is to be secured concerning the utilization of other ions, especially potassium and phosphate, other points of reference more closely connected with cellular metabolic processes must be found. Moreover it must be recognized that ultimately the factors that determine the excretion of even sodium and chloride may be indirectly but nevertheless indissolubly related to these same cellular processes. In both Addison's disease and advanced renal insufficiency the concentrations of sodium and chloride in the serum fall; presumably the renal tubules no longer reabsorb salt in the usual manner. In both conditions administration of extra salt has a beneficial effect, but beyond this the analogy fails. The symptomatology of the two conditions is entirely dissimilar. In Addison's disease, moreover, symptoms and signs may be alleviated at once by the administration of adequate amounts of potent cortical extract without addition of salt. In nephritis, as far as we've been able to determine, cortical extract is without influence upon salt wastage or symptoms.

I say this rather emphatically at this moment because so many people are saying, "Cortical extract controls salt excretion by the kidneys and so we should give it in all states of salt depletion."

In some cases with advanced tuberculosis and in pneumonia, the kidneys often allow salt to escape in an inexplicable manner. From the standpoint of salt balance these patients seem to be indistinguishable from those with Addison's disease. I know no test so far provided to distinguish Addison's disease by the electrolyte pattern without some other clinical criteria.

The symptomatology of these cases is quite different. Administration of salt appears to have little influence upon their condition, or less influence than it has in other cases of salt depletion. We have been able to detect neither clinical improvement nor change of salt balances in these conditions after administration of cortical extract. We are forced to recognize therefore that there must be differences in the significance of salt wastage in these conditions. It has been discovered that during the crisis of Addison's disease, or after the removal of the adrenals from animals, the excretion of potassium diminishes as that of sodium increases. It would be easy to infer, and it was inferred, that the kidney re-absorbs more than the usual amount of potassium, and that the crisis is merely a manifestation of potassium poisoning. However, these crises may come on before the serum potassium has risen appreciably, and bear little or no resemblance to the symptoms of potassium poisoning. The cells seem to be holding excessive amounts of potassium. It was natural to wonder whether the retention in the cells of so much potassium increased their internal osmotic pressure, thus exaggerating the swelling of the cells that resulted from depletion of the extra-cellular sodium.

When this point was examined, Harrison and Darrow found that the cells apparently didn't take up water in response to this excessive load of potassium. This potassium was obviously osmotically inactive. Does it demand a far stretch of the imagination to surmise that the potassium retention is an expression of a derangement of those metabolic processes in the tissue cells in which potassium is involved? Would it seem absurd to consider the failure of the kidney to re-absorb sodium salts as an expression of the derangement of the metabolism of some of the renal tubule cells?

In Addison's disease administration of extra potassium has the most unfortunate effect. But in familial periodic paralysis it was found that administration of potassium salts relieved symptoms. It was thought that the attacks of paralysis were precipitated by the wastage of potassium in the urine, especially when serum potassium proved to be low during attacks of the disease. When the condition was investigated in detail, however, it was discovered that the excretion of potassium during and just before an attack did not increase, rather it diminished, and that the potassium given for the therapeutic purposes was retained without any rise of serum potassium. Apparently something in the muscle cell in familial periodic paralysis creates a demand for unusual amounts of potassium to permit the orderly continuation of the metabolic process.

The study of salt and water balance doesn't need any justification in the clinic at this date but it does need integration with the study of other metabolic processes. And I should like to add again in defense of the clinic that just as the clinic has often led or pointed the way

to physiology in the elucidation of problems of salt and water equilibrium so it need not stand upon the order of its going in this new direction, because experiments are provided every day by disease.

DR. KEYS: I should like, first, to thank Dr. Peters for his discussion and, second, to remind you that Dr. Peters will attempt to answer questions or to discuss specific points which you may raise.

I suspect Dr. Owen Wangensteen may wish to make some remarks on the relation of these questions of water and mineral metabolism to the practice of surgery.

DR. OWEN H. WANGENSTEEN: There are a host of problems which arise every day in the clinic, which are centered in water and electrolyte balance. A number of these are explicable from our present knowledge; many remain a mystery. A number of years ago when I first became interested in the problem of obstruction I happened one day to give some dogs water under the skin and that unfortunately went on for a few days. I learned to my dismay that dogs given water under the skin die. We know that a person can drink water by mouth over a long period of time without taking any food and survive. I've often puzzled over that problem; I wondered how it could come about, whether there is a basal collapse, or what it is.

Problems which concern the surgeons more immediately, of course, are problems which relate to administration of fluids after operation. One thing most surgeons wish for and hope some day to see is a fluid other than sodium chloride which can be given subcutaneously or intravenously. We can use glucose dissolved in water, and it can be given under the skin, but it is a rather painful agent.

DR. KEYS: Dr. Peters, could you attempt to throw some light on those quite difficult questions?

DR. PETERS: I don't know what to say about the dogs getting water under the skin and dying. But I don't think that one can for a moment analyze such a problem in terms of quality. One would at least have to consider terms of quantity. Now the same thing is true also in this surgical procedure; I have been for a long time extremely interested in handling gastric cases.

I have found it peculiarly difficult to penetrate surgery or to do anything with gastro-intestinal cases because there were certain hindrances or conventions. The first one of them was that as soon as the patient arrives some fluid is administered, regardless of other considerations. Therefore, I never had any base line to begin with. So I started off with a condition that no surgeon would ever want to touch, mercury poison, a condition in which the whole gastro-intestinal mucosa is absolutely torn to pieces. I tried to see how much fluid was needed. I also tried to find out what the gastro-intestinal tract could do under those circumstances if you just gave it a chance to do something by itself. I found that if you didn't give such patients any fluid at all by mouth, tube or otherwise, the vomiting and the diarrhea ceased. In fact we had one man who went without vomiting, diarrhea or urination for five days. He seemed to be in pretty good shape and was sitting up reading the paper at the end of that time.

I don't see why people should object to giving sodium chloride. I think the objections to giving sodium chloride lie largely in failing to meet a quantitative equation. Of course, I don't see any reason for attempting to give sodium chloride intravenously to keep up with the surgeon who puts a stomach tube down and washes out the stomach with water. He washes out the chloride faster than I can ever put it in by the skin or veins and we have been able to recover 72 grams of sodium chloride in the washings from the gastro-intestinal tract of a patient in the course of one day while the poor interne was hard put to it to supply chloride in the other direction. Dr. Wangensteen doesn't make this kind of error but it is very commonly done.

In diabetic acidosis, where bicarbonate is low, it may be thought that bicarbonate should be used. However, it won't do the least bit of good to make a completely perfect pattern of the patient's serum if he is still so depleted of chloride and fluid that the total amounts of chloride, bicarbonate, and everything else are far below the normal level. On the other hand, if the patient is given enough sodium chloride and give his kidneys half a chance to work, he can perfectly well adjust this pattern unless he has severe renal disease. The very small

amounts of potassium and calcium required in the serum are being supplied to the patient in more quantities than he needs from all the tissue cells that are being broken down. Apart from these, sodium and chloride make up the whole of the way. Why should I want to give him anything else? Chloride makes up a great part of the anions. Bicarbonate, which is the rest of it, is always available because the patient is continually producing CO_2 in ample amount to make up his bicarbonate. The only trouble is that if you are going to give sodium chloride alone you must make sure you are giving it in proper quantities so that the kidneys will react. Hartman's old experiments prove that. Sodium chloride is the ideal solution because it comes nearer providing everything you need. And if you do not get the proper patterns in the serum of electrolytes as a result don't blame sodium chloride, but blame yourself for having given improper amounts of sodium chloride.

Glucose is given sometimes with sodium chloride and sometimes without. Glucose supplies carbohydrate to prevent the breakdown of carbohydrate metabolism and the acidosis that might result. It is a nutritive material. Water is administered with it also and if the solutions are properly balanced there is available the little extra water needed to provide for his insensible perspiration.

The main thing I should like to bring out is that the patient's urine volume must be followed. It is not necessary to supply enough sodium chloride to make 4 liters of urine a day; you don't have to try to produce edema in a patient who is usually malnourished from lack of proteins. You must see that his kidneys are getting rid of a liter or a liter and a half of urine a day in order that they may adjust the patterns which you can't quite adjust by Hartman's solution or any other expedient. If you want to add a saline plus glucose there is no harm and it provides something to burn. I don't see any reason to give lactate to be burned when CO_2 will form the bicarbonate that you need.

DR. KEYS: The question of water and salt binding by the proteins must remain a key point to be settled before it is possible to discuss water and salt exchanges in the body in a truly quantitative manner. If any appreciable fraction of the water is restrained from its ordinary solvent action by the proteins, then osmotic activity calculations based on total amounts of water and salt must be erroneous. Dr. R. A. Gortner has for some years insisted that some of these matters of the inter-relations of electrolytes and proteins are not as simple as they seemed at one time.

DR. R. A. GORTNER: I was very much interested this morning in Dr. Peters' statement that the Donnan equilibrium did not tell the whole story, and that some of the anions and cations were immobilized. I notice that Dr. Peters didn't use any terms which are common in the colloid literature, but, after all, I think possibly the phenomenon of adsorption may explain certain of these ion inactivations. At least I'm rather convinced that way myself. And as long as we are dealing with surfaces, it's perfectly evident that the state of the colloidal material within the cell, if it is varied at all, will vary the surface exposure and will shift—in my terminology or in the colloid chemist's terminology—the adsorption equilibria which are so characteristic in many cases of potassium as contrasted to sodium. Perhaps the colloid chemist's terminology doesn't tell the whole story but it gives us a certain picture and the change from health to disease can be looked upon to some extent at least, it seems to me, as a change in the physical state of those colloidal constituents which go to make up the protoplasm.

I will admit that our technics of measurement are not adequate for solving many of those problems. But I think that with that viewpoint kept in mind and with the intensive studies of acid-base changes, electrolyte changes and water-equilibrium changes which are being made in so many physiological laboratories, some day we shall get to a point of synthesis where the physiologist and the colloid chemist and the physical chemist all will talk in essentially the same terms about the same phenomena. I am sure that the colloid chemist and the physical chemist and the physiologist are not so much interested in defining the terms in which a physiological process is operating as they are in actually getting down to the facts of the case, and in finding out what is actually going on under one metabolic condition or under a pathologic condition which is imposed upon the normal physiology of the cell.

DR. KEYS: I think that Dr. Peters is star game, and as many times as we can get him on his feet is all to our benefit, in spite of the fact that I am sure that he must look forward with dread to this rather concentrated program that we have for these two days.

DR. PETERS: I want to correct what possibly may have been an error in understanding what I said this morning. If I said that the Donnan equilibrium couldn't explain some of these phenomena and things have been squeezed into it, it was no aspersion on the Donnan equilibrium. I believe that has been established on thermodynamic principles by Gibbs and by Donnan which none of us would dare to question. The only point is that it is only applicable to certain provinces and we've tried to squeeze all kinds of things into it. I think perhaps the best illustration I can have of that is the time when Dr. Van Slyke—and remember I should never cast any aspersions on Dr. Van Slyke—explained the distribution of ions between the red cells and the serum on the basis of Donnan equilibrium. Prof. Donnan was there as the first discussor. He got up and said, "I should never have had the temerity to try to apply my equilibrium to such a complicated system. I am lost with amazement that it can have been so applied—and I am still doubtful."

DR. GERALD EVANS: I am interested in these questions with regard to problems of muscle physiology and of the adrenal cortex. I think it is exceedingly significant that Kendall has separated out several distinct compounds from the adrenal cortex, any one of which when injected into the patient with Addison's disease almost miraculously corrects the disturbance of salt and water metabolism.

Moreover, one of those same compounds has been shown recently by Long and his associates at Yale to be apparently equally potent in another direction, namely, effecting the conversion of protein into carbohydrates. I found that in the absence of the adrenal cortex, protein is not converted into carbohydrate very readily. I took a lot of trouble to find out whether or not the defect preceded the defect of salt metabolism. I found that the protein-carbohydrate conversion was damaged before any of the recognized signs of adrenal failure had appeared, namely, the depletion of sodium elevation, and the potassium and urea increase in the blood.

We might like to think that the protein carbohydrate metabolism determines the electrolyte metabolism. But I can't be sure that that is so. I'm a little bit afraid that the story might equally be the other way around. Of course, that's exactly the point, we are lacking a lot of facts in general physiology.

There is one other point. Although one recognizes that potassium is held within cells and sodium outside of it, we look upon it as a great mystery. We recognize too that phosphates, soluble or inorganic or esters of low molecular weight, are in the fluid. I'd be very interested to have Dr. Gortner's comment on whether phosphate can be in any sense osmotically active and still be held by adsorption to enzyme systems.

DR. GORTNER: Well, yes, a phosphate could still have osmotic activity though held by enzyme systems since in the phosphoric acid the oxygen molecules will attract to themselves water shells, and thus the osmotic activity would be what is heresy to a good many people, that is, a binding or release of colloidally held water. If that in fact can be done, it will also depend, altogether, on what the phosphate is associated with as to whether you have this variable water relation. There may be osmotically active water and osmotically inactive water if you want to put it in those terms. Some water may be more or less fixed to polar groups of the proteins of phospholipins and of all sorts of systems.

Depending on whether those polar groups are exposed toward a free water surface, or whether those polar groups are buried in a colloidal matrix where the free water surface is not so generally available, there will be a shift, it seems to me, in the osmotic properties of the system, even if you have the same number of osmotically available ions. I realize that this hypothesis doesn't have general acceptance by everyone. But I think the evidence is piling up more and more that we must recognize that a considerable fraction of the water molecules are not freely mobile in the presence of the hydrophilic colloids. They maintain a more or less fixed position. More and more types of evidence have been introduced in recent years pointing in that direction and I don't see any

particular qualitative difference between the immobilization of a water molecule on a colloid surface and the immobilization of five molecules of water in the case of copper sulphate. We know perfectly well from a good many physical chemical measurements that ions are hydrated in solution. The massive protein molecules containing the peptide groupings, amino groupings, carboxyl groupings, and so on and so forth, all tend to attract water molecules which lose a certain amount of kinetic energy when they come within their sphere of action. The more recent studies indicate that after all water is a pretty complex system to begin with; that we have actually, at room temperature, fragments of what you might call ice, floating around in ordinary water. If one shifted the equilibrium between polyhydro and monohydro water molecules theoretically there should be a shift to some extent of the osmotic behavior of ions suspended in that particular system.

DR. KEYS: Many of us will remember the ease with which A. V. Hill some years ago disposed of the phosphates in setting up a balance between the red cells and the plasma to account for the osmotic equilibrium as it seemed to be at that time. I think that we are now well aware, of course, of the extraordinary complexity of the system which Hill lumped together as phosphorus expressed as H_3PO_4 with 70% osmotic activity. Today few would venture to make a final balance sheet for the osmotic relation between red cells and plasma. The uncertainty as to the osmotic activity of the phosphates inside the cells is one major obstacle. This is even more true of the muscle cells where the hexose phosphates confuse the picture still further.

In addition to the complexities already mentioned, we must not forget that we seldom have, in the body, the conditions of a true equilibrium. Membranes which are ultimately permeable to a given ion or molecule may offer considerable restraint and thereby slow down the passage of that ion through them. What is the effective osmotic activity of the solution containing that ion or molecule during that time? When large movements of fluid across a membrane are taking place rapidly, even chloride may have osmotic effects where, given time, it would have zero activity. There seems to be good reason to believe that an osmotic buffering action may arise in all systems where membranes are differentially permeable to solutes so that they pass through at different rates.

DR. ARILD HANSEN: I should like to ask what criteria are used for determining the amount of sodium chloride to administer, whether it is a measure of the vascular bed, whether it is excretion, whether it is amount of the gastric fluid which has been removed, or whether it is the clinical picture. We are interested in our department, particularly Drs. John Anderson, Thompson and McQuarrie, in the question of the relationship of sodium chloride to the carbohydrate metabolism as it affects the diabetic. A diabetic child in coma given large quantities of sodium chloride by mouth had a very rapid recovery, but with this rapid recovery was a great increase in blood pressure which went to pathological bounds. Diabetics were placed on a regular type of diabetic diet with vegetables, etc., and were given quantities of sodium chloride varying from probably 5 to 30 grams in a twelve hour period. These individuals exhibited a great decrease in the output of sugar as well as a decrease in the insulin requirement. However, when blood pressure was measured these young subjects were found to have become hypertensive with systolic pressures of 160, 170 and 180. When the potassium salt was used in the same type of study the opposite response occurred.

DR. PETERS: I can't help wondering whether Dr. Hansen is speaking of diabetes in general or certain diabetics. In certain attempts to test the effects of sodium on our diabetics we have not been successful in duplicating these effects.

I can't help for a moment just stopping at one point, and asking Dr. Hansen what he means by potassium to sodium ratio. I don't see any reason for the use of the term ratio or applying it to an entirely independent variable. The term "albumin-globulin ratio" is another case in point. Why not take account of the amount of albumin that is in serum and the amount of globulin? As far as we know in origin, and function and every other respect these proteins are entirely different and their effects on osmotic pressure are different. It makes all the difference in the world whether you've got a high globulin or a low globulin and a high albumin and a low albumin but I

don't see that it makes any difference in the world whether you've got a high albumin-globulin ratio or a low albumin-globulin ratio. We have heard of sodium and potassium ratios, calcium and potassium ratios, magnesium and sodium ratios, and everything else; but as far as we know, the further we go the more we appreciate that these ions all have their individual functions and their particular abilities to perform certain reactions or to participate in them.

Now, to go back to the other subject. Potassium is a dehydrating salt. It is excreted with a great economy of water. We never have been able to get any other salts that have such relatively low concentration in the plasma and such enormously high concentrations in the urine. It is excreted as a foreign body and takes with it a certain amount of water, enough to be dehydrating within limits.

Dr. Hansen asked how we found out that people were hydrated or dehydrated. Well, we can't at the present time. We are peculiarly unable to. I don't believe that we have a method that really accurately measures blood volume in the first place. I think that all plasma volume or blood volume methods measure something in addition. There is very good evidence of that in Smith's old experiments which are so much neglected at the present time when we use spectroscopes, spectrophotometers and all kinds of elaborate instruments. We are becoming more accurate in analysis without considering the fundamental defects in the blood volume system which affect the distribution of the dyes in the blood stream.

Now we have tried at Yale to measure the interstitial fluid, and we are at present trying another method. We are also trying to measure the *total* fluid of the body. I believe all such methods will probably be a little complicated to introduce into the home or a general service. But by the use of such methods we hope to be able to check on the clinical criteria that we now have to use to determine the hydration of the patient. At present you must rely on elasticity of the skin, the general state of the circulation, whether their blood pressure has fallen too far, the serum proteins, etc., but most of all you must look at the patient. No amount of chemistry will eliminate accurate clinical observations. But I say accurate clinical observations with my fingers crossed because I'm not sure how far any of these criteria are really a good indication at the present time. By measurement of the total amount of fluid in the body and the interstitial fluid and observation of the shifts between them, we may be able to check on these things and in a few years be able more accurately to say how much fluid a patient needs.

When you come to giving patients fluid, you give them enough first of all to take care of the depletion they've already undergone, and enough more to enable them to carry on in all functions of the body. Here is the point of looking at the volume of the urine and also at the renal functions behind it. It seems to me a little homely thing that's too often neglected when physicians are apt to ask for a sodium determination that can't possibly be done short of twenty-four hours.

DR. HANSEN: The studies on diabetic children are not my major work but that of Dr. John Anderson here. I saw the observations on eight or ten subjects and saw the general form of the responses I mentioned.

DR. JOHN ANDERSON: I think Dr. Peters may be right that one of the chief defects in our studies was the lack of full balance studies with the several types of salt solutions used.

BLOOD REGENERATION IN THE ANEMIAS

Chairman: DR. HAL DOWNEY
Professor of Anatomy
University of Minnesota

Leader: DR. GEORGE H. WHIPPLE
Professor of Pathology and
Dean of the Medical School
University of Rochester

In a few introductory remarks the chairman called attention to the complexity of the subject, and cited as one of the major problems for future study the reason for the continued normoblastic regeneration in the bone marrow of pernicious anemia on liver treatment, while other normoblastic anemias show little or no response to this treatment. It might be argued that the megaloblasts which are so numerous in the marrow of pernicious anemia during relapse are primarily responsible for the marked reaction of this marrow to liver. While this may be true during the first few days of treatment it does not account for the continuous erythropoietic response after the marrow has become normoblastic, nor for the complete change of the histological structure of the marrow, and the normalized maturation of the neutrophil leukocytes which are so characteristic of pernicious anemia blood and marrow.

Dr. Whipple was introduced at this point and attention called to the great importance of his researches on the regeneration of blood in anemic dogs, this work having led directly to the first trials on the effect of liver in the diet of pernicious anemia patients.

DR. WHIPPLE: Artificially produced radioactive iron is an extremely sensitive agent for use in following iron in the course of its changes in body metabolism, lending itself to studies of absorption, transport, exchange, mobilization, and excretion.

The need of the body for iron in some manner determines the absorption of this element. In the normal dog when there is no need for the element, it is absorbed in negligible amounts. In the anemic animal iron is quite promptly assimilated.

One may choose to believe that the iron absorption is largely a concern of the small intestine and furthermore that the mucosa is the tissue responsible for its acceptance or rejection. It may be possible to show that the epithelium of the mucosa is conditioned by the anemic state of the circulating blood so that absorption of iron takes place. At any rate the curve of iron absorption by the anemic dog indicates that the peak absorption (four to eight hours after feeding) takes place when the food materials are largely in the small intestine. At the end of eighteen to twenty-four hours the radioactive iron is practically all in the colon and no significant absorption of iron is demonstrable. It would seem that the colon is not concerned with iron absorption.

The plasma is clearly the means of transport of iron from the gastro-intestinal tract to its point of mobilization for fabrication into hemoglobin.

The speed of absorption and transfer of iron to the red cell is spectacular. The importance of the liver and bone marrow in iron metabolism is confirmed.

Radioactive iron as ferrous gluconate given by vein enables us to study *iron excretion* in urine, bile and feces.

DR. GEORGE HOYT WHIPPLE of Rochester, New York, has been Professor of Pathology and Dean of the School of Medicine and Dentistry of the University of Rochester since its founding in 1921. Doctor Whipple and Doctors Minot and Murphy of Boston were made joint recipients of the Nobel Prize in Medicine in 1934 for their discovery of the cause and also a successful method of treating the previously fatal disease, pernicious anemia. Other outstanding honors received by Doctor Whipple have been the *Popular Science Monthly* Award and Medal in 1930 and the Kober Prize in 1939.

Doctor Whipple was Director of the Hooper Foundation for Medical Research and Dean of the Medical School of the University of California between 1914 and 1921. Prior to the latter period he had been Pathologist at the Ancon Hospital in Panama and Associate Professor of Pathology at the Johns Hopkins Medical School in Baltimore. He is a graduate of Yale College and received his medical training at the Johns Hopkins Medical School. Since 1927 he has served as a trustee of the Rockefeller Foundation and for several years has been a member of the Board of the Rockefeller Institute of New York. He is a member of the National Academy of Science, the American Physiological Society, the Association of American Physicians, the Society for Experimental Pathology, and other scientific organizations. While his fundamental medical research work has covered a wide range of subjects, his most outstanding contributions have been those pertaining to liver function, pigment metabolism, various forms of anemia, formation and regeneration of the blood proteins, and the diseases of metabolism.

There is an initial extra output in urine and feces during a few days (three to fifteen days) following the iron injection and this may total 2 to 8 per cent of the injected iron. Following this initial reaction the urinary excretion of radio-iron drops to traces or even to zero.

The feces always contain measurable amounts of radio-iron. In five dogs receiving 100 to 250 mg. of radio-iron the fecal excretion per day settled down to 0.05 to 0.4 mg. per day.

Blood destruction by acetyl-phenylhydrazine causes a definite increase in radio-iron eliminated in the feces (0.1 to 1.0 mg. per day). Probably most of this excess iron comes through the biliary tract (bile fistula). The bile under usual conditions contributes very little iron to the intestine (0.01 mg. radio-iron per day or less).

The body controls its iron stores by absorption or lack of it rather than by its capacity to eliminate it. The evidence is overwhelming that the dog excretes iron with difficulty and in small amounts, even in the plethoric state, by means of the biliary and gastro-intestinal tracts.

Perhaps we may hazard a guess as to the capacity of the dog, whether he be anemic or plethoric, to eliminate surplus iron in comparison with the amount of iron in circulation. Dog 37-180, weight 9 kg., had a blood volume of 700 ml. and a total amount of hemoglobin in circulation amounting to 140 gm. (equivalent to 480 mg. of iron). This dog received injections of iron (or red cell equivalent of iron) amounting to 400 mg. of which 130 mg. was labeled radio-iron. The base line of radio-iron excretion was approximately 0.18 mg. per day. If the excretion of labeled iron is typical of the behavior of all surplus iron in this dog this would represent an iron excretion of about 0.6 mg. per day. If this excretion of assumed surplus iron represents the normal ability of the dog to excrete excess iron it would require about two and a half years for the animal to eliminate excess iron, equivalent to the amount in circulation as hemoglobin—evidence of the difficulty of this task for the dog.

DR. C. J. WATSON: Coproporphyrin isomer type I is regularly excreted in increased amount in hemolytic jaundice, and in pernicious anemia during relapse. Splenectomy, or administration of liver extract, respectively, brings about a significant decrease in the amount of coproporphyrin I excreted. This isomer type does not correspond in configuration to the porphyrin contained in hemoglobin, so that there is no reason to believe that the increased amounts are related to the destruction of hemoglobin. On the other hand, there is much reason to consider that coproporphyrin I formation and excretion is correlated, perhaps quantitatively, with erythropoietic activity in the bone marrow. Thus, megaloblasts and erythroblasts, especially in embryonic, and in pernicious anemia bone marrow, have been shown to contain coproporphyrin. Although the significance of this is by no means clear, it appears certain that increased amounts of coproporphyrin I are formed when there is increased erythropoiesis, and this is particularly true in the group of anemias in which hemoglobin formation is not disturbed (the normochromic group, or those with high color index).

The isomeric coproporphyrin III, which does correspond in configuration to the porphyrin of the hemoglobin molecule, is increased in various toxic states, such as poisoning due to lead, arsenic, mercury, sulfanilamide and others. There is much reason to believe that coproporphyrin III is not due to an abnormal destruction of hemoglobin. For example, it has been noted in cases of lead poisoning that an increased excretion of copro-III persists long after the initial blood destructive phase of the disease has passed. It is much more likely that coproporphyrin III formation in lead poisoning is due to a disturbed formation of hemoglobin, perhaps to a blocking of the entrance of iron, into a fraction of the porphyrin intended for the hemoglobin molecule. This view coincides well with the fact that the anemia of lead poisoning is distinctly hypochromic in type, pointing to an associated disturbance in hemoglobin formation. Studies of hemoglobin metabolism in patients treated with sulfanilamide, carried on in association with Spink, have shown that the effect is similar to that of lead in that the anemia is both hemolytic and yet hypochromic. Rimington has found coproporphyrin III in the urines of rats receiving sulfanilamide. This tends to liken further the effects of lead and sulfanilamide upon hemoglobin metabolism, although it should be noted that preliminary studies which we have carried out have not shown such a regular nor marked increase in excretion of coproporphyrin as observed experimentally by Rimington. The

difference may be in the fact that Rimington's rats were given very much larger per kilogram doses than what we employed therapeutically. Further studies of this problem are in progress.

The reticulocytes contain protoporphyrin and this has been identified by Grotepass as belonging to isomer type III, in other words, corresponding to hemoglobin. The function of the reticulocyte protoporphyrin is as yet unknown. Two possibilities must be considered: (1) that it simply constitutes a slight excess of porphyrin intended but not used in the construction of hemoglobin while the cells were yet in the bone marrow, or perhaps to be used for this purpose even after the reticulocytes have gained access to the circulation; (2) that the protoporphyrin serves the rôle of a respiratory enzyme, since it has been amply demonstrated that the reticulocytes have a measurable oxygen consumption, while the mature erythrocytes do not. As yet no evidence is available in favor of one or the other of these possibilities.

The reticulocyte protoporphyrin can not be regarded as the parent substance of coproporphyrin I, because of lack of correspondence in configuration of their molecules. On the other hand, it might very well be parent to coproporphyrin III, and is another possible source of origin for the excess of this porphyrin encountered in lead poisoning and other toxic states, as already mentioned.

DR. CHARLES H. WATKINS: Dr. Downey has asked me to discuss the morphologic changes in the blood associated with blood loss. In any condition in which there is chronic blood loss, whether relative or absolute, the erythrocytes are hypochromic but the total number per cubic millimeter of blood is normal or only slightly reduced. The individual erythrocytes are paler than normal owing to a decrease in hemoglobin concentration in the cells; anisocytosis of moderate degree is usually present although extremes of variations of size of cells are not uncommon; polychromatophilia is usually increased slightly above normal and consequently the percentage of reticulated erythrocytes is usually slightly increased. Ordinarily the leukocytes are unchanged in number and appearance. In cases of long standing iron deficiency the hemoglobin may be much reduced and under such circumstances the erythrocytes may contain only a very faintly staining ring of hemoglobin around the periphery of the cell, a condition known as anochromasia. When the hemoglobin is reduced to this extent the erythrocytes per cubic millimeter of blood are usually decreased but not in proportion to the decrease in hemoglobin. There is evidence of slight increase in erythropoietic activity; the myeloid leukocytes are relatively unchanged.

In acute blood loss the picture ordinarily is quite characteristic. There is a rapid reduction in the hemoglobin as well as in the number of erythrocytes per cubic millimeter of blood. Morphologically there is evidence of increased regenerative activity and increase in polychromatophilia; the percentage of reticulated erythrocytes is higher than normal; anisocytosis is more marked with regenerative macrocytes much in evidence. Normoblasts may also appear in the peripheral circulation. Usually there is moderate leukocytosis with the increase largely in polymorphonuclear neutrophils. If the hemorrhage is very severe, immature myeloid leukocytes may appear in the peripheral circulation, resulting in a leukemoid reaction. The blood platelets are usually increased in number in severe hemorrhage. During the recovery phase, hemoglobin regeneration ordinarily falls behind the production of erythrocytes so that hypochromic anemia occurs.

A thorough morphologic study of blood smears is of value in all cases of anemia in order to eliminate, if possible, a primary blood dyscrasia. This examination also proves of value in determining the degree of hemopoietic activity at a given stage.

It is fortunate that in most cases of secondary anemia the cause is obvious but in obscure types identification of the etiologic factor may be difficult. Frequently obscure forms of secondary anemia are due to chronic loss of blood from the gastro-intestinal tract, which may be persistent or recurrent. The bleeding may be due to malignant lesions, benign polypoid tumors, or benign ulcers of the gastro-intestinal tract. In some instances relatively slight bleeding from hemorrhoids may produce secondary anemia of marked degree. It is certain that treatment of secondary anemia should not be instituted without a complete study of the patient and not until a satisfactory etiologic factor is found. Investigation of secondary anemia frequently entails de-

tailed examination and if this is slighted a serious disease may pass unrecognized, particularly if the blood responds to the treatment given. In addition to complete roentgenologic examination of the intestinal tract, examination of stools for occult blood should be made, for often bleeding lesions of the small intestine can be recognized only by this means. Examination of stools for occult blood should be done over a period of days, for frequently bleeding is of a recurrent type and of relatively short duration. If blood is found persistently, abdominal exploration may be advisable provided there are no features of a primary hemorrhagic blood dyscrasia.

CLINICAL PROBLEMS OF THROMBOSIS

Chairman: DR. E. T. BELL
Professor of Pathology
University of Minnesota

Leader: DR. CHARLES H. BEST
Professor of Physiology
University of Toronto

DR. BEST: Dr. Gordon Murray has established that heparin is useful in certain types of vascular surgery—in embolectomy and anastomosis of blood bessels. He has had a number of cases of embolectomy and thinks that success has been greater in those in which heparin has been used. Dr. Radvin reported a case of a young doctor who had a coronary attack and then had a mural thrombus which lodged as an embolus in the aorta. This was removed and the blood vessels sewed up in the usual way. Heparin was used and the doctor is now back at work.

It is not proved that heparin is absolutely necessary, but the use of it apparently helps. Dr. Murray has also reported a case in which he resected 4 inches of the popliteal artery and inserted the same length of the patient's jugular vein; heparin prevented thrombosis at the site of sutures. There has thus been definite success in the use of heparin in vascular surgery. It is proved that heparin can be given to the patient without danger. There is interest in the use of heparin in subacute bacterial endocarditis. Several clinics are following Dr. Kelson in his lead of using sulfapyridine and heparin together.

It is easy to show, as Dr. D. Y. Solandt and I have done, that coronary thrombosis can be prevented in animals.

DR. BELL: If you are trying to prevent postoperative thrombosis, how often would you administer heparin?

DR. BEST: Only one way—continuously. Over 400 cases in Toronto have been heparinized over the so-called "danger" periods. Heparin was used continuously for over four weeks in one case.

DR. MOSES BARRON: Over how long a period were the 400 patients heparinized?

DR. BEST: One to four weeks. The period varies. Usually it is about seven to ten days.

PROFESSOR CHARLES H. BEST is today one of Canada's outstanding medical men and one of America's best known men of science. In 1922, when he was only twenty-two and while still a medical student at the University of Toronto, he collaborated with Dr. F. G. Banting in a Nobel Prize winning research, the discovery of insulin.

With world wide renown at such a youthful period, some thought Charles Best would rapidly disappear from the scientific horizon. They were wrong. The high place in the world of science which Dr. Best has today is certain evidence that the scientific curiosity and ability which drove him to collaborate in the discovery of insulin were not a fly-by-night "lucky break" but the mark of inborn competence. After graduating in Medicine from the University of Toronto in 1925, Dr. Best went to England where he worked in the Physiological Laboratories of Professor C. Lovatt Evans and Sir Henry H. Dale. Later, when the chair of Physiology became vacant at Toronto, the University authorities wrote to England, in search of a bright young Englishman. The reply was sharp and to the point. They were told the most outstanding young physiologist of the day was on their own doorstep. Thus it was, that in 1929 Dr. C. H. Best became Professor and head of the Department of Physiology, University of Toronto.

Extending his scientific interests beyond the sphere of sugar metabolism, Dr. Best has made significant studies on histamine, choline and other biologically potent substances. He, with collaborators, isolated histamine from the liver and later demonstrated an enzyme, a ferment found in the body capable of destroying this highly toxic substance.

Recently Dr. Best's interests have turned toward the processes involved in the clotting of blood and the methods used in preventing clot formation. His studies have found their application in efforts to prevent thrombosis of various sorts.

DR. BELL: Dr. J. S. McCartney will speak on the danger period in postoperative thrombosis.

DR. MCCARTNEY: The period of danger varies tremendously. If you are thinking of the time in which embolic lesions are liable to occur, most of them occur within the first two weeks. There are occasional instances where the fatal embolism has occurred within twenty-four hours after operation, and a few in which the embolus has taken place two to three weeks subsequent to the operation. There is the question of how long it takes a large thrombus to form.

DR. BEST: Fifteen minutes. We have seen a thrombus big enough to close the aorta form in fifteen minutes. The platelet thrombus forms first, and once the blood stream is slowed or completely stopped, then clotting and thrombus formation occur with great rapidity. Once the thrombus has formed, heparin has no effect.

DR. BELL: How far in front of the embolism does the thrombus form?

DR. MCCARTNEY: There is good reason to believe that it will go beyond the next branch.

DR. BEST: In a series of experiments on dogs, Dr. Solandt and I opened the pericardium, tied off the descending branch of the left coronary artery, infiltrated sodium ricinoleate so that it would lie against the endocardium, sewed up the chest and started heparin immediately. The thrombus formed before we could get out of the chest.

In the dog you can tie off the coronary arteries and not get any mural thrombus. In the dog, tying off a single coronary artery does not lead to thrombus formation if the endocardium is not injured.

DR. BELL: It seems obvious that if we knew how far the thrombus formation precedes the detachment of the thrombus, we would be in a much better position to advise therapy.

DR. MCCARTNEY: Most patients who have thrombophlebitis do not get embolic lesions. There are a few patients who have it and then have the embolism let loose and cause either infarcts of the lungs or fatal embolism.

DR. BELL: Some lasting two to three months do that. You think that the reason why there is only a small percentage of clinical thrombosis which results in embolism is that the thrombi are adherent?

DR. MCCARTNEY: The clinical thrombophlebitis requires complete closure of the vessel. Those with embolism do not have complete occlusion.

DR. F. J. HIRSCHBOECK: Are there any criteria as regards age, obesity, etc., for cases in which you wish to use heparin? When do you begin using it?

DR. BEST: Some surgeons operate under a moderate heparinization. Dr. Murray says to use it from two hours to five or more hours after operation; this depends on the operation. They have started after splenectomies in an hour or so. When clotting is complete there is no reason to suppose that bleeding will recur. If there is a bleeding point, bleeding will be increased by heparin. Heparin is used in prostatectomies, splenectomies, etc.

DR. HIRSCHBOECK: Dr. McCartney, most of the thrombi form during the healing period, but now the belief is that the emboli that cause trouble break off rather early.

DR. MCCARTNEY: Statistics show that many patients who die of a massive embolism have had emboli earlier with or without symptoms.

DR. HIRSCHBOECK: Is the danger chiefly during the first two or three days or the second, third or fourth weeks?

DR. MCCARTNEY: I think it is in the early period.

DR. REA: Dr. Best, how do you give heparin to the patients? Have you noticed any hemorrhagic tendency?

DR. BEST: In dogs we give an initial injection of about 30 to 40 units per kilogram, then a steady injection to keep the clotting time at twenty minutes or higher. There is no way of telling what the clotting time of the patient or dog will be, *i.e.*, there is great variation in the reaction to heparin.

DR. BELL: Can you neutralize the effect of heparin?

DR. BEST: You can precipitate all of the heparin out of the body with protamine. This was first shown by Chargaff and Olson. Protamine should not be used clinically at present.

DR. PAYNE: When will the price of heparin get down so it can be used for clinics and hospitals inexpensively? I understand that recently the local use of heparin has been recommended. Two or three years ago, Dr. Olson in New York was working on a synthetic compound similar to heparin; what is your reaction to such substitutes?

DR. BEST: Heparin is being made in Toronto at the Connaught Laboratories; the process was worked out by Scott and Charles. The details of the process have been published. It takes large amounts of lung to get a gram of heparin. The initial cost was $12.50 per 100 mgm. It is $2.70 now. Two vials a day is the average amount.

With regard to regional heparinization and general heparinization, it is thought to be much better to heparinize generally than locally. It is far less expensive to do local heparinization, but it seems a little unreasonable. Synthetic anticoagulants have been made. They are cheaper but are much less effective and are much more toxic.

DR. BELL: The next topic is the influence of age on the formation of thrombi.

DR. MCCARTNEY: This is based upon the findings in our postmortems and what has been gathered from the literature. In a number of papers there is a marked discrepancy in the incidence of pulmonary embolism as reported both from series of operations and also from series of postmortems. They vary anywhere in the postmortems from 0.5 per cent to 12 per cent. This does not appear to be reasonable. It means either that the postmortems were not carefully done or that there was some difference in the material in various series. In order to get some of the background of the incidence of thrombosis and embolism, I went back to early literature and found that Virchow in the 40's made a study of seventy-six consecutive postmortems and found eighteen thromboses and eleven embolisms of the lungs. With regard to the question of age—if we stop to think of it a moment, there are practically no thromboses in children except when related to definite infectious processes, such as otitis media. When you get to older people there are plenty of instances of thrombophlebitis where there is no suggestion of any infectious process at all. In our postmortems not only the incidence of venous thrombosis increases with age until you get up into the eighth decade, but the incidence of pulmonary embolism also goes up in the same way. Each instance of pulmonary embolism presupposes that there is a thrombus somewhere. The actual incidence of thrombosis is several times that of the incidence of pulmonary embolism whether you consider the fatal cases or the nonfatal, where it is an accident and an entirely unsuspected condition. I gathered a large number of reports of operations at various sites because we have always felt that there were certain operations which were likely to be followed by thrombosis and embolism. The pelvis and lower abdomen have been particularly mentioned. Appendectomy was mentioned frequently as an operation which was rarely followed by embolism. Most appendectomies are done before thirty years of age (76-80 per cent). Practically no emboli occur in these early decades. In later decades primary appendectomy is not infrequently followed by emboli. Practically no prostatectomies are done until after fifty years of age and then the incidence of thrombosis and embolism is very high. Hernias run practically a straight line through all decades and in the later decades most of the embolic lesions take place. Gynecologic operations reach their peak along about the fifth decade; not many are done before the age of thirty. In our material the incidence of embolism seems to be about as high after transurethral resection as after a suprapubic or perineal prostatectomy. One of the prime factors in the development of thrombus and embolus is the mere opening of the abdomen and the resulting splinting of the abdomen and the change in respirations. The question of age at which the operation is done more than the actual point of operative procedure should be considered.

DR. BELL: It is, then, not the operative site

but the age of the patient that gives thrombosis and embolism. Formerly it was thought that it was the operative site.

Shall we say something about the rôle of infection in thrombosis? Some years ago it was taught that there cannot be a thrombus without an infection. We have gotten away from that idea entirely. There still remain, however, a good many thrombi which have an infectious origin.

DR. MCCARTNEY: In the postoperative thrombosis and embolism, if it is the idea that the infection is at the site of operation, this simply won't stand scrutiny because most of the postoperative thromboses and emboli have no relation to the site of operation whatsoever. There are some cases, naturally, where they are related, but in many of them it is difficult to see how infection can spread from the site of operation to the veins of the pelvis or lower extremities, where the primary thrombosis is found.

DR. T. A. PEPPARD: We have considered thrombosis and embolism as a postoperative, post-traumatic and obstetrical complication. This should be mentioned as a medical complication and mention made of certain influences, such as pneumonia, and its occurrence in cardiac failure.

DR. MCCARTNEY: With the material here, the incidence in the medical group is a little lower than the post-traumatic, but this is due to the lopsidedness of the material. When you get to the higher decades, it becomes much more frequent in the people with heart disease and is several times as frequent in the medical cases as in the traumatic and postoperative cases.

CURRENT TRENDS IN PUBLIC HEALTH*

Chairman: DR. GAYLORD W. ANDERSON
Professor of Preventive Medicine and Public Health
University of Minnesota

Leader: DR. THOMAS PARRAN
Surgeon General
U. S. Public Health Service

DR. PARRAN: In observing the current trends in public health many questions immediately arise as to the paths along which these trends are taking us. It is important to stress at the outset that no one knows the answers to these many questions that confront both the public and the many agencies created by the people for the protection of their health. It is only by full and frank discussion of these questions and problems that rational means of solution may be evolved and subjected to trial.

It is obvious that the problems of public health today are very different from what they were several years ago. That was the time when the health officer was the man who was supposed to tack up a sign when a case of scarlet fever occurred, and after four weeks to return and take it down. His duties in the interim were few and equally simple. That was also the era in which the problems of the practitioner of medicine were likewise simple. He could carry in his little black bag most of the materials he used in the practice of his art and in his head he might carry most of the medical knowledge of his time. Our knowledge of man and dis-

DR. THOMAS PARRAN, JR., is a native of Maryland. He was graduated from the Georgetown Medical School, receiving his degree at the age of twenty-two in 1915. He entered the United States Public Health Service in 1916 immediately beginning on a rather meteoric career. By 1918 he had been made Chief Medical Officer at Muscle Shoals. In 1919 he was transferred to Washington as Executive Officer in the Medical Division of the War Risk Insurance Bureau. After serving here for two years the United States Public Health Service transferred him to the midwest where he spent four years with the Missouri and Illinois State Health Departments developing local health work. In 1925 he returned to Washington to take charge of the venereal disease control work of the United States Public Health Service, a position that he occupied for five years. In 1930 the position of Commissioner of Health of New York State became vacant due to the resignation of the former Commissioner to enter a different type of work. Governor Roosevelt feeling that there was in the state no person who seemed particularly suited for this position at the moment requested the detail of an officer of the United States Public Health Service to serve as Commissioner in New York for a period of years. Dr. Parran was detailed to this work serving with distinction as Commissioner until 1936. That year he returned to Washington as Surgeon General of the United States Public Health Service succeeding Dr. Cummings who had reached the retirement age.

*The discussion here published is not verbatim but contains the essence of the speaker's statements as reported by the chairman.

ease was very restricted for the scientific laboratory had not yet made much progress in the evolution of elaborate tests and therapeutic armamentarium.

Today we find that all of this has changed. Just as the developments of science have added to our knowledge of disease so have they also created problems of prevention. Public health has made great advances in the control of certain specific diseases, notably the infections. It has been relatively simple to control typhoid through attention to the water supply, to prevent diphtheria through immunization, to limit the development of simple goiter through the ingestion of iodine. But with the control of certain specific diseases others over which equally effective control has not yet been established stand out in greater prominence. At times we have been so engrossed with our successes in one direction that we tend to lose sight of equally great problems in other directions.

The attack upon some of these is in large measure a problem of creating individual understanding and participation. Only a few of the public health problems can be solved by such simple expedients as putting a few drops of chlorine in the water. In public health work it is extremely important that individual members of the community should both understand the problems and participate in their solution, for the health of any community is the sum of the health of the individual members of that community. This has meant that those actively engaged in public health work and especially those in public health nursing have had to become teachers.

Another difficulty has arisen from the fact that the prevention of certain diseases necessitates the treatment of the individual. In some instances, as in syphilis and tuberculosis, the treatment has been necessary to diminish the likelihood of spread as well as to benefit the infected individual. In other instances medical service has as yet given us no effective means of prevention, but only methods of treatment to restore the patient to health. Yet it is just as important to the community to restore the sick patient to health as it is to safeguard him from becoming ill. Thus step by step in the development of public health as the simple problems of health have been solved and our attention turned to the more complex problems of community protection we have become more and more concerned with the manifestation of disease and the necessity of its treatment. We have realized that in our attempts to approach an ideal with respect to both personal and community health we must give attention to the alleviation of those diseases for which we have as yet no effective prevention. Just as the community attempts to safeguard its citizen through its licensing of qualified medical practitioners, so society, which must pay for the ravages of disease, turns to a consideration of all measures which will reduce human suffering and the economic burden from sickness and avoidable death.

During the past years in which we have witnessed unparalleled progress in the science of medicine we have seen an equally signficant progress in public thinking about the application of this science. It is very true that medical science has "sold itself" to the public. Certainly the public of today is more interested than ever before in the changes that are occurring within our science. At the same time they are asking themselves to what extent these scientific findings can be put to more effective use and can be made more generally available so that their benefits may reach a greater number of persons. People are demanding that this knowledge which is ours be put to work promptly and widely for the use of all.

On the other hand we have seen some reluctance on the part of medicine to respond to this public demand. This reluctance has not been conditioned by any basic dislike to respond in those fields where the health of the public may be benefited. Yet there has been a very real concern over some of the methods that have been proposed for putting medical science more widely to work. In the various proposals a few salient points of controversy stand out.

Any attempt to bridge this gap between the scientific laboratory and the application of its findings to the health of the nation raises immediately the question of financing. If it is to be a measure of public concern and is therefore to be supported by taxes, there occurs immediately the situation that those who depend on public support receive more than do those who attempt to buy their own services. There is the important problem of distribution of medical care without the danger of too great political control. No one has as yet evolved a simple formula

which will solve these and countless other allied questions, nor is it likely that any formula will be found without the benefit of trial and error. It is necessary in approaching this social problem that we use the same type of experimental method which has given us the principal discoveries of medicine in the laboratory. Unless we experiment with various methods we will learn nothing and no progress will be made in the better application of the findings to the solution of some of our most pressing public health problems. Fortunately we have in our form of government forty-eight or more different experimental laboratories in which we may try out various plans that may be proposed, learning what is good from one and retaining it while discarding that part of another which has been found to be bad. Just as medical progress rests on experimentation so also does social progress.

The national health survey was an attempt to find out and measure some of the health problems of the country so that we might formulate rational plans for trial. It represents the most comprehensive approach that has ever been made to the many problems affecting the nation's health. From the findings of this survey and the proposals of the Interdepartmental Committee there evolved a national health bill. While this bill, the so-called Wagner bill, has many serious defects in its present form, these defects can be remedied. Little can be accomplished by paying money out of several unrelated brackets with no central planning and no adequate review of the needs of the program as a whole. We cannot have a unified health program if we build hospitals with funds from one source, operate them with different funds, use still different funds for the health of the children, others for the medical care of the indigent and still others to protect the health of the worker. It is unlikely that any program that lacks coördination of direction can be successful.

In the execution of any plan for solving current public health problems through the furnishing of more nearly adequate care, two factors are essential. The first of these is trained personnel; without trained and skilled workers, experiments are unlikely to succeed. The other essential is that whatever federal participation is included shall not mean too great federal control or domination. Within reasonable limits the individual states should be allowed to work out their own methods and procedures. It is only by this freedom of planning that we can look forward to that degree of experimentation that is needed and the development within different states of programs best adapted to the local needs. So long as we can have experimentation we may hope for the evolution of practical plans to meet the increasingly important new challenges of the public health.

In the discussion that followed the informal remarks of Dr. Parran, President Ford and Dr. J. C. McKinley commented on the necessity of including problems of mental health. Dr. Parran agreed that all phases of the prevention and care of mental diseases were an essential part of the broad health program of a community and pointed out that such were included in the study and plan of the Interdepartmental Committee.

Dr. A. J. Carlson, commenting on the basis of acquaintance with the situation in the Scandinavian countries and Russia as well as this country, spoke of the importance of so planning that the individual would pay to the extent of his financial capacity. He stressed the dangers of creation of a plan that might tend to relieve the individual of any thought of personal responsibility and to develop a philosophy of utter dependence upon government. Dr. Parran concurred in believing that whatever plan was tried should provide that patients who are able should pay in proportion to their ability. This may lead to a system of insurance to prepare for such costs, possibly including levies upon employer as well as employee. The success of hospital insurance has created new interest in this possibility.

Other participants in the discussion included Professor Stuart Chapin, Dr. H. S. Diehl, Dr. A. J. Chesley, Dr. G. F. Amyot, and Mr. H. A. Whittaker.

CHEMOTHERAPY

Chairman: DR. ARTHUR D. HIRSCHFELDER
Professor of Pharmacology
University of Minnesota

Leader: DR. PERRIN H. LONG
Associate Professor of Medicine
Johns Hopkins University

DR. HIRSCHFELDER: We are celebrating the Fiftieth Anniversary of the Medical School; but though it is only a little past the thirtieth anniversary of the initiation of chemotherapy by Ehrlich's introduction of salvarsan for the treatment of syphilis, we might also celebrate the anniversary of that event. It is about twenty-eight years since Morgenroth with the discovery that ethyl-hydrocuprein exerted a specific action against the pneumococcus conducted the first chemotherapeutic attack upon bacterial diseases. In 1912 I found that although ethyl-hydrocuprein was effective against pneumococcic septicemia in mice it would not cure pneumococcus pneumonia in rabbits and Chesney and others showed that it would not cure human pneumonia. It is interesting that now the workers at the Mellon Institute have carried Morgenroth's work one step further and are finding that hydroxyethylapocuprein which is less toxic than ethyl-hydrocuprein has a definite curative value in human pneumonia. But the great revolution in the chemotherapy of bacterial diseases came a very few years ago when Domagk introduced prontosil and the French experimenters showed that the sulfanilamide portion of the molecule was the part that produced the chemotherapeutic effect. Our distinguished guest, Dr. Perrin H. Long of Johns Hopkins was the first to introduce sulfanilamide in America, and he and Dr. Marshall by introducing methods of precision into the use of this wonderful drug, and the related substances, have done the most to add to our knowledge of how they act and just how they should be administered. I have the honor of introducing Dr. Perrin Long.

DR. LONG: The average case fatality rate in lobar pneumonia in the Johns Hopkins Hospital during the past few years has been 20 per cent. Despite the use of new and more effective anti-pneumococci sera, the case fatality rate has not been appreciably lowered during the last three years. During the past year, since July 1, 1938, following the use of serum and sulfapyridine and sulfapyridine alone, the case fatality rate in pneumococcal infections in the Johns Hopkins Hospital has been cut to 7.2 per cent. This is the lowest in the history of the hospital. Since July 1, 1938, we have treated thirty-one patients with anti-pneumococci serum, eight with serum and sulfapyridine and 126 with sulfapyridine alone. In this group of patients, two were suffering from pneumococcal infections in which the pneumococci proved to be resistant to sulfapyridine therapy both in the clinic and in experimental animals. It has been shown that sulfapyridine given by mouth may be irregularly absorbed by different individuals and also that certain individuals acetylate the drug to a high degree. Hence, therapy with sulfapyridine by mouth is more difficult than when sulfanilamide is used. It has been our practice in adult patients to use the following dosage schedule. As soon as the diagnosis of pneumonia is made, the patient is given 4 grams of the drug in a single dose, then 1 gram is given every four hours until the temperature has been normal for forty-eight hours, then 1 gram every six hours until resolution is well under way, and finally 0.5 grams four times a day until the lungs are clear. It has been our practice on the day following the admission of a patient to the hospital to give the sodium salt of sulfapyridine by the intravenous route if the patient's temperature is not below 101° by rectum and the concentration of free

DR. PERRIN H. LONG is associate professor of medicine at Johns Hopkins University, in charge of the bacteriological division of the Department of Medicine. Dr. Long graduated in medicine from the University of Michigan in 1924. During the period from 1927-29, he was first assistant, then associate at the Rockefeller Institute for Medical Research in New York. Because of his valuable contributions in the field of infectious disease, he was then invited to become a member of the department of medicine at Johns Hopkins University. First as an associate and later, after promotion to the rank of associate professor, Dr. Long continued to carry on important investigation in clinical bacteriology and infectious disease. He was the first to point out to the medical profession in the United States the value of sulfanilamide in the treatment of various infections, notably those due to the streptococcus. His intensive research and numerous publications dealing with various aspects of sulfanilamide therapy have been of major importance in quickly bringing this valuable remedy into general use.

sulfapyridine in his blood is below 4 mgm. per cent. If such is the case, a single dose of sodium salt of sulfapyridine based on 0.06 grams per kilogram of body weight and made up in a 5 per cent solution in distilled water is given by the intravenous route. This dose will raise the blood concentration of sulfapyridine by about 5 mgms. per cent. If a patient is severely ill on entry into the hospital, we generally start therapy with an intravenous dose of sodium sulfapyridine based on 0.06 grams per kilogram. This may be repeated in four hours if necessary. Oral therapy is carried on as previously outlined with the exception of the omission of the initial dose. A further example of the effectiveness of sulfapyridine and sodium sulfapyridine in pneumococcal infections may be gained from the experience of Dr. Horace Hodes of Sydenham Hospital in Baltimore. During the past year, he has treated seventeen cases of pneumococcal meningitis with sulfapyridine given by mouth alone or in conjunction with the sodium salt administered by the intravenous route. Of these seventeen patients, eight have recovered. Of those patients who have recovered, seven were treated with the sodium salt by the intravenous route as well as by sulfapyridine. It is our practice now to establish blood concentrations of 15 to 20 mgms. per cent in pnemococcal meningitis by administering an adequate amount of the sodium salt of sulfapyridine by the intravenous route. This concentration is maintained until the temperature has been normal for from twenty-four to forty-eight hours. Oral therapy is also started as soon as is possible. Sodium salt of sulfapyridine cannot be given by the intraspinal route because it causes a severe myelitis which is frequently fatal. It can only be given by the intravenous route.

DR. GEORGE E. FAHR: Can the administration of alkali prevent hematuria and formation of stones?

DR. LONG: Theoretical consideration would lead one to believe that if the urine was kept very alkaline, pH 7.5 to 8, that the precipitation of acetyl sulfapyridine crystals would be decreased. Hence it would be less likely that renal stones would be formed.

DR. ERLING S. PLATOU: May the drug be used by the intrathecal route?

DR. LONG: Never by the intrathecal route.

DR. FAHR: You can usually tell very promptly if the treated patient is going to make a quick response to sulfapyridine.

DR. LONG: That is our experience. Improvement comes rapidly and should be marked within forty-eight hours. During the past year, we have had a large experience at the Sydenham Hospital with pneumonia secondary to measles. In this type of measles, sulfapyridine is highly effective and as Dr. Hodes has reported the drug brings about a spectacular improvement within thirty-six to forty-eight hours.

Dr. Hodes has also reported that the drug is of definite value in the therapy of whooping cough pneumonia. Some one has asked me if the drug is valuable as a prophylactic agent. Only under exceptional conditions should sulfanilamide or sulfapyridine be used as a prophylactic agent. Our experience leads us to believe that the only instance of proven prophylactic value of sulfanilamide is in the treatment of crushing wounds and compound fractures. In these types of injuries, the administration of sulfanilamide in full prophylactic doses prevents gas bacillus infections and facilitates markedly the healing of the wounds.

DR. FAHR: On account of the fact that Dr. Bieter found that too large doses causes too high blood levels in mice which was harmful to the mice, I keep the blood level of sulfapyridine in my patients at about 5 mgms. per 100 c.c.

DR. THOMAS MYERS: Do increases in the concentration of the drug in the blood increase the incidence of toxic effect?

DR. LONG: Not as far as we know. We have noted that children are more prone to develop leukopenia when they are receiving sulfapyridine than is the case when sulfanilamide therapy is being used.

DR. DONALD C. CREEVY: How about postoperative pneumonia?

DR. LONG: We employ sulfapyridine in our patients in whom the clinical diagnosis of pneumonia has been made, so this includes the postoperative pneumonia. We feel that if an attempt is made to make a definite bacteriological

diagnosis before instituting treatment that valuable time will be lost.

DR. FAHR: What has been your experience in trying to retype pneumonia in the course of sulfapyridine therapy? We have sometimes found it difficult to retype the organisms found in the sputum.

DR. LONG: This has not been our experience. We do not feel that sulfapyridine therapy interferes with the subsequent typing of pneumococci in the sputum.

DR. CREEVY: Do you use sulfapyridine in the urinary tract diseases?

DR. LONG: We have not used sulfapyridine because of its high acetylation rate in the urine.

DR. MYERS: When would you stop treating a case of otitis media?

DR. LONG: We think it best to continue sulfanilamide for at least two weeks after a complete clinical cure has been effected. During this period but small doses should be given. We have had very few mastoids develop in our nose and throat patients ill with hemolytic streptococci otitis media since we instituted the routine use of sulfanilamide in the treatment of this disease. It is of importance when continuing treatment to watch the white blood cell count. Acute hemolytic anemia generally makes its appearance within the first five days of therapy with sulfanilamide, while agranulocytosis most frequently occurs after ten days of therapy and generally from the seventeenth to the thirtieth day of treatment. Hence it is important to follow the white blood cell count as long as sulfanilamide therapy is being continued.

DR. HAROLD N. WRIGHT: The present intense interest in the chemotherapy of bacterial diseases must, necessarily, carry over some of its advances to other forms of chemotherapy, and particularly to the treatment of protozoan and metazoan infections, especially the treatment of syphilis.

One of the important facts brought out in the clinical use of sulfanilamide in the treatment of pneumonia is the necessity for maintaining an effective concentration of the drug in the blood stream throughout the period of treatment.

The usual plan of antisyphilitic treatment with arsenical drugs, namely eight to ten injections at five to seven day intervals, requires at least eight to ten months continuous treatment in order to render the disease non-communicable.

Following a single intravenous injection of one of the arsphenamines an effectively spirocheticidal concentration of the drug can be maintained in the blood stream at best for a matter of hours.

The avoidance of toxic reactions, particularly the cumulative effects of the arsphenamines, has been the principal reason for the comparatively discontinuous form of therapy. It is true, of course, that the complete excretion of a single dose of any of the arsphenamines may require fourteen to twenty-one days. The prolonged retention of these drugs is, however, closely connected with their colloidal properties, the therapeutic properties being roughly inversely proportional to the degree of colloidality. I see no reason why it should not be possible in the not too distant future to manufacture the arsphenamines in such a way that their antisyphilitic properties may be enhanced from four to ten times, in all probability with less danger of cumulative effects than at present. Mapharsen, which probably possesses no colloidal properties whatever, we have found in rats to be 80 per cent excreted in the first twenty-four hours.

Hyman and his collaborators in New York appear to have shown that much more rapid disappearance of the symptoms of early syphilis can be obtained by practically continuous intravenous infusion of the arsphenamines for a period of five days, the disease being rendered non-communicable and 86 per cent of the cases becoming seronegative in an average time of twelve weeks. Although this work is still only in the experimental stage, it points to the necessity for further investigation of the optimum conditions for the administration of arsenical antisyphilitic drugs.

DR. N. K. JENSEN: In all compound fractures treated at the General Hospital since March of 1938, we have placed sulfanilamide powder in the wounds upon the completion of debridement. The wounds have then been closed with skin sutures only, and the fractures completely immobilized. To date seventy-five fractures have been so treated. Infection has occurred in only four of these wounds, giving a percentage of infection of 5.3. In the first forty-

one cases so treated, only one wound became infected. These cases were reported in the journal *Surgery* for last July. Two of the wounds that became infected were so extensive that satisfactory closure could not be accomplished due to loss of skin. In another instance, the patient had a recurrence of his compound fracture eight days after injury while maniacal in delirium tremens. The fourth infection occurred in association with internal fixation of a compound fracture of the ulna; our only attempt at internal fixation of a compound fracture. No gas gangrene or tetanus infection has occurred, and the infections have been mild.

Before the use of sulfanilamide locally, the incidence of infection in compound fractures treated at the General Hospital during the last five years ranged from 26 to 30 per cent. In 1937 alone, five patients developed gas gangrene. The statistics for each year previously have shown approximately the same incidence. Besides these cases developing gas gangrene, it has been found necessary in the past to perform several amputations each year because of infections resulting from compound fractures.

We have found that by local introduction of sulfanilamide powder directly into the fresh wound, the concentration of the drug in the extent of the wound can be maintained at levels approaching saturation (800 mgm. per cent) for approximately thirty-six hours. Experimental study in animals reveals that an equal amount placed directly in a contaminated wound is much more effective than given parenterally at a separate site. In this series of patients reported no other sulfanilamide therapy was used.

Dr. King's findings that a small amount of autolyzing tissue inhibits the action of sulfanilamide suggests that all devitalized tissue must be removed from the wound. This we have found to be true, both in our clinical and experimental study.

Dr. Joseph T. King: The group using tissue cultures in the study of the effects of the sulfonamide compounds on the streptococcus includes Dr. Henschel, Mrs. Green and myself.

We have observed that strains of beta streptococcus grow in tissue culture clots in two forms. Some strains grow as dense colonies showing no diffuse periphery, while the colonies of other strains show a dense center and wide diffuse periphery. This periphery is not composed of long chains of streptococci but of single organisms or small groups of two or three.

The response of the two colony types of sulfanilamide differs. In the living state, at a magnification of 60×, the compact type of colony shows no characteristic qualitative change; it is simply smaller. When the colony with diffuse periphery is treated with sulfanilamide the normal periphery is completely inhibited. Occasionally such an inhibited colony will show a few long, thick chains growing, usually from a small segment of the periphery. In older cultures one may rarely find a colony showing a complete periphery of such chains. Such a periphery is easily distinguished, even in the living state, from a normal diffuse periphery.

On the basis of colony diameter the inhibition is more striking in the case of strains whose colonies grow with diffuse peripheries. One can hardly escape the impression that the drug inhibits the invasion of the clot by the organisms.

It has also been observed that effects of sulfanilamide are antagonized by the products of tissue disintegration. If small fragments of fresh, sterile tissue are planted in tissue culture clots inoculated with a suitable dilution of a strain of beta streptococci showing diffuse peripheries, it has been found that sulfanilamide fails to produce typical inhibition of the periphery of those colonies close to the fragment while colonies further away show the expected inhibition. Not all tissues are equally effective in producing this "release" of colonies from sulfanilamide inhibition. There is evidence, however, indicating that even those tissues which are least effective in preventing the qualitative response do interfere with the bacteriostatic property of sulfanilamide. Studies on this point are in progress.

It was shown by Lockwood that peptones reduced the bacteriostatic effect of sulfanilamide for the streptococcus. Hoyt and Levine found that peptones interfered with the bacteriostatic effect of sulfapyridine on the pneumococcus.

The adsorption experiments of Larson, Bieter, Levine and Hoyt suggest that peptones and certain amino acids interfere with the adsorption of sulfapyridine.

It is evident that such products would be liberated by tissue undergoing proteolysis, and, while the precise mechanism by which such substances interfere with the activity of the sul-

fonamide compounds is not entirely clear, it is important to realize that disintegrating tissue protects the streptococcus from the action of sulfanilamide.

DR. RAYMOND N. BIETER: In our work on chemotherapy using Type II pneumococcus in mice, we have come to believe that the following factors are important and are to be considered:

1. Compounds or a series of compounds of related or unrelated chemical structure should be studied in a sufficient number of mice of the same strain to be statistically significant. To help answer the question of how many mice are necessary for one experiment, we have made use of the studies of Halvorson and Ziegler. They have attempted to show how the change in error varies with the number of times an experiment is repeated. Their experiments consisted of a study of bacterial growth in vitro. They have found that if one goes from a relatively few experiments up to about 30 repetitions, a rapid decrease in the percentage of error due to chance occurs. Above thirty the decrease in error due to chance takes place much slower. In other words if an experiment is repeated thirty to forty times, chance is eliminated to a high degree, and in order to get a marked improvement over thirty to forty repetitions of an experiment, one must go well up into the hundreds.

2. When chemotherapeutic drugs are used clinically they must be used against a wide variety of strains of a single organism. Therefore, it behooves investigators to study the actions of these drugs on as many strains of a given organism as possible. It is well known today that sulfanilamide has a more marked action on certain strains of the beta hemolytic streptococcus than in others. Undoubtedly this effect will be noted with this and other drugs acting also on other bacteria.

3. For the most quantitative results, surely it is agreed that the dose of infecting organisms given to an experimental animal should be described in terms of the organism's M. L. D. (minimum lethal dose). For mice this can be easily determined by simply injecting a suitable number of these animals. It is our belief that the M. L. D. in terms of dilution alone is not enough, but that these inoculations be paralleled using an organism count. Many different multiples of the M. L. D. are used by the investigators, but as yet no one knows the optimum number of M. L. D.'s to use. In most of our work, we have used from 4,000 to 8,000 M. L. D.'s of our Type II pneumococcus.

4. The age of the culture used for inoculating mice or other animals is perhaps of paramount importance. It is well known, for example, that a culture of pneumococci aged from eighteen to twenty-four hours can be more easily phagocytized by human leukocytes than a younger culture. This difference may result in a different chemotherapeutic picture in the experimental animal. In our work with the Type II pneumococcus, we have adhered to the principles laid down by Chesney, Ward and Ender, and Neufeld and Handel. That is, actively growing young cultures are most resistant to phagocytes, and when explants of these cultures are made, maximum growth occurs. Alternate passage through mice and artificial media assures uniform virulence. An eight-hour culture satisfies the conditions of maximum virulence and no lag in growth.

5. The experimental technic best suited to each organism should be worked out and used for each bacterium. For example, in pneumococcus infections in mice, it appears to us that the subcutaneous method of inoculation is superior to the intraperitoneal method. This is believed to be true for the following reasons:

a. Human pneumonia for the most part is a localized infection. The subcutaneous inoculation of mice with Type II pneumococcus results in a localized infection in the mice lasting about twenty hours, as compared to less than one-half hour following intraperitoneal inoculation.

b. This then results in a in vivo experiment more equivalent to the average speed of a human pneumonia infection.

6. To obtain data most satisfactory for statistical treatment, the death times of mice should be determined quite accurately. We have, therefore, determined the death rates in our mice more or less on an hourly basis. In addition, by this method, smaller differences between chemotherapeutic substances can be noted which would not appear on a day to day determination of death rate.

7. In all of our work to date, we have employed the method of drug administration by simply mixing the pulverized drug with ground food and giving it to the mice in waste-proof food cups. This method has several advantages.

a. It is very simple and easy to use.

b. When the mice are once inoculated, no further handling is necessary. We have found that repeated handling of mice interferes with their food intake. Therefore, when mice are injected repeatedly with a drug, the element of starvation may play a rôle.

c. We have found that mice eat quite regularly during six hour periods both day and night. Their food intake is greater during the night than during the morning. Other than for this variation, their food intake tends to run quite uniform per twenty-four hours after the first day or two. It requires one or two days for the mice to become accustomed to the food cups and thereby assume their maximum food intake per twenty-four hours. By weighing the food at twenty-four hours or shorter intervals, the drug intake can be easily computed. Inasmuch as Marshall and his collaborators have found that a mouse eliminates a given dose of sulfanilamide in about six hours, we believe that our method of food plus drug administration is superior to all other forms of drug administration unless the drug is given at intervals of six or fewer hours. Further reason of the efficacy of drug administration is to be found in the results we have obtained with sulfanilamide and its derivatives on Type II pneumococcus infections in mice. These results can be briefly summarized as follows: With 0.5 per cent of each of the following drugs in the food cups of 50 mice, each showed the following survival rates at thirty to sixty days.

a. Control group..... 0 survivors
b. Neoprontosil ..... 6% survivors
c. Sulfanilamide .....20% survivors
d. Sulfapyridine .....44% survivors

The question of why survival rates in inoculated mice uniformly seldom approach 100 per cent has interested us very much. Undoubtedly a number of factors in the animal body of which we know little play great rôles. One of these has to do with the temperature of the animal. This is especially important because of the observations of White to the effect that when the temperature in vitro studies is raised above 37° C., the bactericidal effect of sulfanilamide and its derivatives becomes greater. We have first of all constructed a micro-thermocouple using a copper constantine junction. This is made small enough so that it can easily be inserted beneath the mouse's skin. The mouse is held in the left hand as if one were to make an intraperitoneal inoculation. In a large series of normal mice, we have found that their normal temperatures most often run between 100 and 101° F. If now a group of mice are given an intraperitoneal injection of our Type II pneumococcus, the temperature begins to drop at about five hours and then thereafter shortly drops precipitously to about 85°. On the other hand, when the organisms are given by subcutaneous inoculation, the temperature begins to drop at seventeen to twenty hours and soon thereafter drops precipitously. As can be seen, the time elements correlate with our observations on blood stream invasion. It should be noted that at no time have these mice shown an elevated body temperature. Another factor that we have found is that mice appear to be very susceptible to environmental temperature changes. For example, mice placed in an environment at 37° C. show a 2° F. rise in half an hour. In addition to these preliminary findings, we have also collected the following preliminary observations:

a. Control mice inoculated with our Type II pneumococcus and placed in an incubator at 37° C. die more rapidly than if kept at room temperature.

b. Mice on 0.5 per cent sulfanilamide in the food and placed in the incubator show a more rapid and greater death rate than an equivalent number of mice maintained on the same amount of drug at room temperature. The sulfanilamide intake in both groups was approximately the same. We know further that normal mice and mice on sulfanilamide in the food maintained in the incubator showed no toxic effects. These experiments in the incubator were conducted with from 15,000 to 20,000 M. L. D.'s of our Type II pneumococcus per mouse. It can be seen, therefore, that

the survival rates or therapeutic effects at 37½° C., that is in the incubator, are not as good as in mice at room temperature. In other words, these results do not all parallel the in vitro observations of White.

Dr. Wesley W. Spink: At the University Hospital, we have been interested in certain toxic manifestations of sulfanilamide and sulfapyridine.

In association with Drs. C. J. Watson and I. Vigness, the problem of cyanosis due to sulfanilamide has been studied. Spectroscopic analyses of the bloods of several of these patients showed that in every instance the cyanosis was due to the presence of methemoglobin and, rarely, sulfhemoglobin. The intravenous administration of a 1 per cent solution of methylene blue to these cyanotic patients was followed by the disappearance of the cyanosis, and the characteristic absorption band of methemoglobin was found to be absent in their bloods. Methylene blue had no effect upon sulfhemoglobin. We have quantitated the amount of hemoglobin converted into methemoglobin in patients with cyanosis by spectrocolorimetric and spectrophotometric methods. In markedly cyanotic patients as much as 30 per cent of the hemoglobin was found to be present as methemoglobin. Clinical observations lead us to conclude that sulfapyridine seldom causes cyanosis. The blood of one patient with a slight degree of cyanosis was found to have 7 per cent of methemoglobin. After methylene blue had been given, the cyanosis abated, and methemoglobin could no longer be demonstrated in the blood.

Dr. Watson and I have studied the pigment metabolism and liver function of patients receiving sulfanilamide and sulfapyridine. Using quantitative methods, we have found that the majority of patients receiving therapeutic doses of sulfanilamide or sulfapyridine for several days will develop some anemia. In some patients it is of marked degree. It is of interest that this anemia is of macrocytic or normocytic hypochromic type. This, in conjunction with the usual finding of a very significant increase in feces urobilinogen, indicates not only an increased destruction of erythrocytes, but a disturbance or retardation of hemoglobin formation. An analogous situation is found in lead poisoning. Sixteen patients receiving sulfanilamide developed jaundice. We have not observed jaundice in any patient to whom sulfapyridine was given. We regard jaundice as an indication of liver dysfunction. In addition to the jaundice, the Van den Bergh reaction was prompt or biphasic, and the serum bilirubin was elevated. Further evidence of liver dysfunction was the increased excretion of urobilinogen in the urine. Jaundice was not observed in any patient who received less than 3 grams of sulfanilamide a day. We have not encountered any patients where extensive liver damage due to sulfanilamide alone was the cause of death. However, four of our patients had serious hepatic injury because of infections, and we are certain that sulfanilamide therapy accentuated the process, and hastened a fatal outcome. We are very reluctant to give sulfanilamide to any one with jaundice, and have done so only in a few instances. For the most part, the liver dysfunction is only temporary, and returns to normal after sulfanilamide therapy has been stopped.

Dr. E. N. Cook: We are all greatly interested in the opportunity to hear Dr. Long discuss the use of sulfanilamide and its derivatives in the field of chemotherapy. In the short time allotted to me today I wish to call your attention to the excellent results we have obtained in the use of sulfapyridine in the treatment of gonorrhea.

The usual gastro-intestinal upsets so frequently seen when this drug is administered are greatly diminished in our experience, because of the fact that in most cases we use only 45 grains daily, and by splitting the dose and giving it with milk each time these untoward reactions have been very infrequent.

We have used sulfapyridine in the treatment of the acute and chronic Neisserian infections with equal results. Almost always the discharge disappears in three to five days, and as soon as this takes place it has been our custom to begin local therapy, including massage of the prostate. With no other form of therapy have we seen such spectacular results as we have noted in patients suffering with gonorrhea who have been treated with sulfapyridine. In no instances have we seen blood dyscrasias, but on two or three occasions when giving a second course of the drug we have noted a dermatitis similar to that seen when sulfanilamide is administered. In

each case it cleared up rapidly upon discontinuing the sulfapyridine.

If the 45 grain dosage does not bring about the expected results in five days, we would advise increasing the dosage to 60 grains daily and continuing it for a period of seven to ten days in addition to the previous five days of therapy with the smaller dosage. English observers have stressed the importance and value of local therapy in conjunction with sulfapyridine by mouth.

DR. ERLING S. PLATOU: With the collaboration of Dr. Wallace Sako and Dr. Paul Dwan I have treated two hundred cases of scarlet fever with sulfanilamide at the Minneapolis General Hospital in the past two years. The drug was usually administered orally in initial doses of 0.05 grams per pound of body weight per twenty-four hours and maintenance doses of 0.03 gm. in twenty-four hours. The dosage was usually decreased but the drug was continued for an average of twelve days. In patients with nausea or severe toxemia we gave the drug subcutaneously in the form of the one per cent solution in sodium chloride. It is our impression that, per unit of weight, children tolerate the drug better than adults. With the exception of the development of leukopenia in two cases and fever and rash in two additional cases in which we were compelled to discontinue the use of the drug, no serious complications were encountered.

In 1938 we reported the results in 100 treated cases, compared with 100 control cases which were admitted to the hospital during the same period. In our treated cases the rate of recovery from the acute toxemic phase of the disease (six days) was no more rapid than in the controls (six days). The patients treated with sulfanilamide did not show prompt subsidence of toxic symptoms such as we have observed following the administration of serum. However, in the cases treated with sulfanilamide the incidence of complications was only 8 per cent, as compared with 41 per cent in the control series. We believe that the best results were obtained when sulfanilamide was continued during the entire convalescent period and that early discontinuance of the drug was the cause of the appearance of complications in a few of our cases.

Since 1938 we have treated 100 additional cases with sulfanilamide, and the incidence of complications remained the same as in the previous series. During this period we have seen a number of rather severely complicated cases to whom physicians had given adequate dosage of sulfanilamide early in the disease only to discontinue it when the temperature reached normal. Continued therapy for at least twelve days has proved to be effective in preventing such eventualities.

Sulfanilamide also seems to have a prophylactic effect in preventing the development of scarlet fever. We have given therapeutic doses for seven days to ninety-four intimate "contacts." None of them developed scarlet fever but three developed severe cervical adenitis. None of the contacts who received both convalescent serum and adequate sulfanilamide treatment developed either scarlet fever or its complications, but we have seen seventeen cases of scarlet fever which developed after the prophylactic use of sulfanilamide in inadequate dosage.

CLINICAL ASPECTS OF THE VEGETATIVE NERVOUS SYSTEM

Chairman: DR. FRANK C. MANN
Professor of Experimental Medicine
The Mayo Foundation, Rochester, Minn.

Leader: WALTER B. CANNON
Professor of Physiology
Harvard University

DR. MANN: We are very fortunate in having with us as the leader of this discussion the man who has done probably the most of any other from the physiological standpoint, in giving a certain amount of basis for the clinician's viewpoint that the vegetative nervous system does have something to do with clinical medicine.

Now there are many titles by which I could introduce the leader of the discussion. I might introduce him as a home-town boy, because we are all happy to own him as a Minnesotan. I might also introduce him as the first roentgenologist, because historically that would be a true title to give him. However, I shall introduce him as I have always thought of him since the time I first entered physiology and studied the fine type of work he did on the pylorus and the use of the x-ray for visualizing the gastro-intestinal tract, namely, as the professor of physiology of Harvard University. Professor Cannon.

WALTER CANNON: I've had very little experience with round tables; I've seen round tables of various shapes; I think this is the strangest shape of a round table that I've ever come across. A round table, I presume, is given that name because it was expected that there would be a sort of family feeling among those who are gathered, and that the discussion would be an informal one.

In order that we may be reminded of the subject under discussion, I'm going to ask for the first lantern slide which will present a diagram of the autonomic system. Here are the central axis, the spinal cord, the cranial division above the medulla, the sacral division below the sacral enlargement of the cord, and the thoracico-lumbar divisions between the sacral and the brachial enlargements. On either side, of course, there are the chains of ganglia connected by the preganglionic fibers with the spinal cord, and the post-ganglionic fibers reaching out to the nictitating membrane, to the heart, to the liver, to the stomach and intestines, and to the adrenal medulla which, as you know, produces a substance imitating in its effects all the effects which are brought about by sympathetic nerve impulses. So we may regard this as a sympathical adrenal system.

DR. WALTER B. CANNON of Harvard University is the accepted dean of American physiologists. For the last forty-one years, ever since his first publication in the very first issue of the *American Journal of Physiology* in 1898, on the movements of the stomach as observed by means of Roentgen rays, Dr. Cannon has made outstanding contributions to physiology which have been of tremendous significance in the development of medicine, pharmacology, and psychology. His major interest has always been the influence of the autonomic nervous system on the functions of the organism, which has led him from control of the stomach through emotion, hunger, surgical shock, exercise, and homeostasis to his most recent achievement: the discovery of humoral transmission at the endings of the sympathetic nerves. This year he has been honored by his fellow scientists, who elected him president of the American Association for Advancement of Science.

Now we are to be concerned mainly today with the functions of this sympathical adrenal system in relation to clinical interests. You will find in a book by Miller, a rather large compendious work, these nerves referred to as layman's nerve as if they were absolutely necessary for life. The next lantern slide will show you a cat with her two kittens. Here she is with her paw lifted, her teeth showing, her ears back because a dog is barking at her; there's no hair rise here because the conveniences for hair rise are up here on the chart. This is the sympathetic system of this cat. Here are the two chains from the superior cervical sympathetic ganglion on either side, here down to this other ganglion in the upper part of the thorax, then the splanchnic coming off here to the celiac superior mesenteric ganglia and the sympathetic—and the abdominal chains reaching down to the pelvis. There is the possibility of these ganglia to some degree being omitted if the chains were taken out in piecemeal as in this case, so we devised the method of taking them out whole as the next lantern slide will show. Here are the two—here are chains taken out complete from the stellate ganglia high in the chest down to the rim of the pelvis. These are the splanchnics

coming off here. What inference can we draw from that situation? In the first place it proves that there is no danger to life.

In the next lantern slide is a cat from which the sympathetic system was removed entirely and this photograph was taken of the cat three years after the system had been taken out. There is no danger to existence in removal of any part of the sympathetic system because these experiments show it's possible to remove the entire system and individuals continue to live for an indefinite period. It is true not only of horizontal animals like the dog and the cat but also true of monkeys that take the upright position.

Furthermore, it is compatible with growth. This system is often spoken of as the vegetative system, and the implication there is that it is concerned with growth. We have, however, removed the system on one side from kittens and allowed them to grow to adulthood and then examined carefully various organs which are bilaterally symmetrical in size; and in those circumstances have not been able to find any difference on the two sides as a consequence of the absence of the sympathetic on one side and its presence on the other.

That's another point which can be made; it's quite possible that operations on the sympathetic might be done on young children and there'd be no danger doing that sort of operation because of fear that growth might be interfered with. It is not interfered with.

It is compatible with reproduction in the female, as the next lantern slide will show. Here is a bitch from which the sympathetic is removed and this is one of nine offspring. There is a rather infantile uterus as a consequence of removal; and there is a serious defect in lactation. This animal had a litter of nine puppies and this is the only one that survived; and it survived because it was particularly vigorous and by pressing and tugging and sucking it managed to get enough milk so that it lived to an age which allowed it to drink milk from a pan. The others all succumbed. The nipples of the dog were hard and dry and the only substance which could be got from them was a very thick creamy substance. As soon as this pup was able to drink milk the curve of growth which we had followed immediately began to rise sharply and it wasn't long before it had reached the usual growth curve of the growing dog.

Apparently when the sympathetic control of the blood vessels of the mammary gland is absent there is a failure of the blood vessels to dilate during nursing and therefore the fluid which is used to carry out the substantial part of the milk is not present and the young, therefore, do not get the nourishment which they should have. Operations on the thoracic part of the sympathetic are very likely to have serious effects so far as lactation is concerned. Then there is a defect which results when the sympathetic of the male is removed from the lower abdominal region.

Bacq, working in the Harvard laboratory, clearly showed that in rats and in rabbits the mating processes would occur in the male up to the point of ejaculation, and at this point there was failure, so the males were sterile. That observation was apparently not known by some surgeons and operations were performed which resulted in precisely that effect in human cases. A point which, of course, ought to be clearly kept in mind when the sympathetic system is interfered with.

It is quite possible to have the entire sympathetic system out of the picture and still have a fairly normal blood pressure. That was first shown by Bradford Cannon, my son, in the Harvard laboratory and later was confirmed by Phemister and collaborators in Chicago. The next lantern slide will show their record in which there was complete sympathectomy and you observe that after the final operation the blood pressure varied between 100 and 120 millimeters of mercury.

In a dog it is quite possible for the animal to exercise vigorously within a short time after the sympathetic has been removed without any serious fall of blood pressure. In a cat, this does not occur at once. The next lantern slide will show what happens; if there is struggle the blood pressure falls instead of rising. Here is a typical rise of blood pressure which accompanies vigorous muscular activities; but in the cat, there is a fall. The same thing happens in the dogs in the first week or so after removal of the sympathetic, but after that a recovery takes place and the animal may exhibit even the violent, vigorous actions of fighting with a perfectly normal dog without showing any signs of defect so far as blood pressure is concerned. This, of course, is if the entire sympathetic is removed.

I don't believe that there would be any serious interference with blood pressure in man on removal of a very considerable part of it.

Now there is another effect which is interestingly related to old clinical observations and that is the effect of the sensitization of the smooth muscle which is deprived of its sympathetic control. Here are the contractions of the nictitating membrane in response to various amounts of intravenous injections of adrenalin diluted 1 to 100,000. This is immediately after resection of the right cervical sympathetic and the removal of the left—the removal of the left ganglion here and the section of the right pre-ganglionic fibers above. At the end of fourteen days the same doses which previously produced these effects now produce these effects. You observe on the side from which the superior cervical ganglion was removed, the smooth muscle nictitating membrane of the cat gave a very much larger response than it did before and to a lesser degree there was a magnification of response on the other side where the preganglionic fibers had been severed. Now the superior cervical ganglion was removed on this side and fourteen days after the second operation, twenty-eight days after the beginning, you observe that there was a greater effect here, indicating a greater sensitization on that side.

The next lantern slide will bring out these same facts graphically. This is a course of sensitization of the smooth muscle of the nictitating membrane, with a consequence of removal of the post-ganglionic fibers, the direct innervation; and here is the effect of merely cutting the pre-ganglionic fibers, disconnecting the smooth muscles from the central nerve systems but still having it connected with the fibers coming out from the superior cervical ganglion.

Now, you observe that the results are similar to that produced by the ganglionic removal on the other side.

Now, that's a very important observation because of the fact that when an operation is done on the sympathetic there still remains the adrenal gland which I called your attention to earlier as the source of a substance which is capable of stimulating the smooth muscle which is affected by this adrenalin given off from the adrenal medulla.

There is a case on record that occurred at the Massachusetts General Hospital. A surgeon was very much interested in a patient, a woman, who had Raynaud's disease. He had removed the ganglia connected with the muscles that were in spasm and the contracted blood vessels of the fingers had changed from being blue, cold, and painful to a condition of being warm and pink, and comfortable. He took a lot of medical students, strange medical students, to the patient's room shortly thereafter, and with a good deal of dramatic vividness he described the operation which had been performed. And then in order to have a good show he swept down the coverlet to show this hand and there it was as blue and cold as it ever was. He was very much chagrined and went back to the office and told the tale. It happened that Norman Freeman, a young surgeon who had spent a couple of years in our physiological laboratory recognized the possibilities and suggested that he take another look. He went back and looked at the fingers and there they were nice and warm and pink again. Well, then they introduced into the veins of this patient adrenalin at the rate of its ordinary production in times of excitement, and the fingers turned blue; or if they gave insulin and caused a discharge of adrenalin from the adrenal medulla, again the blue, or cold condition appeared.

Now what the surgeons are doing at the present time is not to remove the ganglia directly connected with the smooth muscle of the blood vessels but they cut the pre-ganglionic fibers which run out from the central nervous system to the ganglia so that there is a separation of the muscles from the central nervous system, and there is not so great a sensitization of the smooth muscles to the circulating adrenalin.

Now from the experience which we've had in the laboratory, there is only one defect to that situation and that is the possibilities of regrowth. The pre-ganglionic fibers, as we've learned to call them, are cholinergic fibers; that is, they give off at their terminals acetylcholin and the post-ganglionic fibers to the blood vessels are adrenergic fibers and they give off at their endings adrenalin. You cannot connect adrenergic fibers to cholinergic fibers. You can, however, connect cholinergic fibers of any sort with any other. For instance, cholinergic fibers of skeletal muscle can be connected with these

ganglia and they will then operate. If, therefore, you disconnect the nerve of the smooth muscles by cutting the post-ganglionic fibers, the fibers beyond the ganglia, there is no possibility of regrowth. On the other hand, if you cut the pre-ganglionic fibers almost any other fiber in the neighborhood will make connections there and it is very characteristic of the ordinary preganglionic fibers to make the connections which they've had previously.

Repeatedly, we have had occasion to note connections with the celiac ganglion and the upper part of the abdominal cavity after we've cut the splanchnic nerves and even cut out a considerable part of the splanchnic connection; and recently we've shown that the nerve fibers coming through the stellate up into the inferior cervical ganglion will regrow through several centimeters of empty space, even after efforts were made to prevent precisely that thing happening. That's something that ought to be looked into. This regrowth is so remarkable that it almost seems as though there were courses which the nerves took in spite of everything that you did to prevent regrowth taking place.

There's been a good deal of talk about periarterial sympathectomy; that is the possibility of removing sympathetic control of blood vessels by cutting through the outer layers of blood vessels. Along the length of the blood vessel there may be a slight enervation up and down but not to a great degree. The effect, therefore, when this is done is a local one.

Another matter of considerable interest, clinical interest, that's been brought out by operations in complete sympathectomy, is the differentiation between two types of hypertension. You've all become acquainted with the hypertension which is produced by the application of the Goldblatt clips reducing the amount of blood flow into the kidneys. Now that's a type of hypertension which is not affected by complete sympathectomy. Freeman, whose name I mentioned earlier, and Page have shown that after that sort of hypertension, you may call it renal hypertension, has been produced you can remove the entire sympathetic system without altering the hypertension to any degree whatever. Or you can take an animal like this dog that I showed you without any sympathetic system in it, and apply the Goldblatt clips and produce typical hypertension.

On the other hand, the next lantern slide will show that if the carotid sinus nerves are severed and the depressor nerve is cut there develops a hypertension, in this case running up from approximately 120 millimeters of mercury to the neighborhood of 300, a hypertension which persisted here, as you observe, for many months, for two years; when the entire sympathetic system was removed from this animal, the blood pressure came down as you observed to normal limits. So you must learn somehow to distinguish between hypertension of renal origin and hypertension of some other sort before having any rational occasion for operating.

There is no good evidence of sympathetic control of skeletal muscle. For some years operations were done on the sympathetic system in order to diminish the tone of skeletal muscle. That was done on the assumption that the sympathetic had an important effect in maintenance of muscular tones. Royal, whose name is associated with that interest, came to the laboratory and I presented him with an animal with the lower abdominal sympathetic removed on one side, and I said, "You test the knee jerks and tell me on which side the sympathetic has been removed," and he made the test and told me that he couldn't tell.

There's no better test than that, it seems to me, to show whether there is or is not a sympathetic control of muscular tone, and the test when put up to the person who has made the claim had such results that he couldn't tell the difference.

Then there is a further matter that ought to be perhaps considered in connection with a somewhat thoughtless removal of control of the adrenal glands. The adrenal glands are very important agents for liberation of sugar from the liver. We recently got evidence that it's only by the circulating adrenalin or by the substance given off from the liver or blood vessels, sympathin, that sugar is liberated from the liver. And if normal animals with a normal innervation of the adrenals are given insulin, this is usually per kilo, you observe that the convulsions from hypoglycemia occurred in only one instance and then after three and a half hours of endurance of the hypoglycemic condition which might result from the insulin injections. In animals with the adrenals inactivated, that is with the sympathetic supply severed on one side and the adrenal removed on the other, similar

doses of insulin, smaller in most instances, brought on convulsions in all but three instances and these convulsions occurred in the neighborhood of about an hour and a half after the insulin was injected.

Those are the main points which I would call to your attention from experimental observations on animals deprived of the sympathetic system and now I suppose the meeting is to be turned over to someone else.

DR. MANN: I should like to call on Dr. S. Marx White for discussion of the medical aspects of the problem.

DR. WHITE: To me Dr. Cannon's presentation is as those he has so many times made before, of extreme—not only importance, fundamentally—but interest. The clinician, of course, has no right to discuss the experimental side of this unless he makes himself an experimental physiologist, and yet the clinician must be something that many of us were, in my student days at least, a pseudo-physiologist. He must at least listen with a great deal of care to what the physiologist has to tell him.

Dr. Cannon's application of his study to the problem of hypertension, for instance, brings into the discussion one of the fields in which very active interest is manifested today, on the part of the physician and of the surgeon. Those of you who are interested in the development of our knowledge of hypertension, may recall a very interesting discussion which Volhard gave as long ago as ten years in discussing the different types of hypertension. And to me it is of extraordinary interest to see that the physiologist has brought out now by experimental work that Volhard had previously emphasized from inductive reasoning. Volhard, if you will remember, divided roughly, for the purposes of clinical discussion, hypertension into two groups which he divided into the red and the white hypertension.

Now I remind ourselves of that because to my mind it has a very interesting bearing on the problem that we are concerned with in medicine today, one of the problems of the possibility of effective surgical approach upon essential hypertension. If all this is true, and the application in animals and its analogies in man seem to make it so, then the usual surgical attack on the malignant type of hypertension would seem to be directed at the wrong point; because there are many facts which make it probable that the malignant hypertension is a type in which a humoral mechanism has come into play, the arteries of the kidney having been involved up to the point where some substance, possibly elaborated in the kidney, possibly related to what some writers have called rennin, and what not—a humoral substance is elaborated. Dr. Cannon brings out the combinations that can be brought about by surgical operation. I remember having heard a few months ago of the experiments to which he has alluded by Anley and Herring; both produced a hypertension by ablation of the connections of the carotid sinus. They then caused a disappearance of this hypertension by removal, complete removal, of the sympathetic nervous mechanism and then followed this by the use of Goldblatt clamps and again produced hypertension; the conclusions of these writers, on the basis of accuracy of these experiments were that this form of hypertension at least, was humoral in origin. The kidneys possibly are the source.

If all this is true, and there is much to make us believe that it is so, then if we are to indulge in an attack on the problem of hypertension from the surgical standpoint, it drives us back to the surgery of the benign, so-called essential, benign hypertension. Many of us physicians believe that such an attack as that is probably unnecessary but it may be that we'll come to just such an attack as that; but for the present it seems to me that our attack is probably along the line of teaching these individuals the proper adaptation to their environment from the affective, so-called emotional, side.

Now if I have a minute, there is one other reference that I would like to make, and that is to a part of the autonomic mechanism to which Dr. Cannon has not addressed himself—and that is to the carotid sinus as a pit of this autonomic mechanism. The knowledge that has been acquired of the means, the modes, by which the carotid sinus can be stimulated has added very greatly to our means of diagnosis in heart diseases. The recognition of certain types of syncope in which there may be slowing even to asystole on the part of the ventricles, dropping blood pressure or some form of cere-

bral reflex which causes syncope, and our knowledge along this line, too, enables us to recognize these cases. We can by stimulation of the carotid sinus, under the finger, reproduce the symptoms and in certain cases where the malady is severe enough, the carotid sinus can be disconnected. But also our knowledge of the effects of the carotid sinus as a part of this regulatory mechanism aids us very greatly in that we can in many instances abate tachycardia and can help often in the diagnosis in the type of mechanism that is occurring not only with but without electro-cardiographic recording. I am just mentioning these very few brief points concerning the knowledge of the autonomic mechanism so marvelously brought out by the physiologists in recent years which aid us in medicine.

DR. MANN: Professor Visscher will now discuss some of the less appreciated results of activities of the vegetative nervous system.

DR. VISSCHER: When Dr. Mann first asked me whether I would contribute to this round table discussion I hesitated a number of days because I felt it would be presumptuous on my part to suggest that I could really contribute anything worthwhile. On considering the question a little further, it occurred to me that there were some points in which the autonomic nervous system had come into some of our observations on aspects of physiology that would not seem to be immediately connected with that subject; and I have rather surmised that those who are experts in the field of autonomic nerve physiology would probably slip over, or at least not be as concerned with these mechanisms, as some of us who look upon the autonomic nervous system as something less than our major interest. It occurred to me on considering the things I've been interested in the last few years, in which some autonomic nerve effects have come into the picture, that I might profitably refer to one or two of them. In view of the time, I shall refer to only one.

In studying the process of absorption from the small intestine, we've been interested in the ability of the intestine to move substances against concentration gradients, placing solutions of mixtures of sodium sulphate and sodium chloride, in isotonic solution in the gut. Over the period of a very few minutes, fifteen to thirty in the waking dog with surgically prepared loops, the sodium chloride concentration in these loops will fall to very low values—perhaps one per cent or just a few per cent of the blood levels for these constituents. Dr. Dennis made the very interesting observation, it seems to me, that a few dogs on whom these surgically prepared loops were made just simply did not show absorption from the intestine when they were made to lie on the table, quietly, without being tied down, and that, instead, the volume of fluid in the loops of intestine, these surgically prepared loops, increased. Well, now to make a very long story short, we anesthetized these dogs and found under anesthesia their intestinal loops absorbed fluid just as well as other dogs. And it came out that these were dogs that were very excitable. On inspection of the mucosa of the exposed loops we found that when they were placed on the observation tables the mucosa was blanched and white and obviously there was diminished or perhaps very little blood flow. It was an emotional reaction probably mediated by autonomic nerves, and if we had more time I should like to ask Professor Cannon some questions on this point but I shall not do so because there are two people who must have some time on this round table program.

I would like to make this observation, however, which comes out of my thinking in connection with talking to this group—that there are undoubtedly very many physiological reactions in the carrying out of which we cannot afford to ignore the importance of the autonomic nervous system in the real life situation. When one sees in such a simple matter as the absorption of water and salt from the intestine, the effect of the sympathetic nerve stimulation, which was undoubtedly the mechanism in this case, it cannot be doubted that more complicated processes that are going on in the alimentary tract are likewise involved. We know they're involved, of course, and this happens to be simply a very striking demonstration of that involvement.

DR. MANN: Some of the more recent clinical work on the subject will be discussed by Dr. B. T. Horton.

DR. HORTON: Dr. Mann, Dr. Cannon, ladies and gentlemen, As I listened to Dr. Cannon's

presentation, I could not help but think of a saying which I learned in high school that comes from Shakespeare, many of you will remember it, when I quote it: "There are more things in heaven and earth, Horatio, than is dreamt in our philosophy." And I have a feeling that there are more signs and symptoms in clinical medicine and surgery produced by the autonomic nervous system than have yet been recorded in our textbooks and in our medical journals. I could not help but wonder as Dr. Cannon showed the picture of his cats without a sympathetic nervous system what the human individual would do or how he would behave if the sympathetic nervous system were removed. Certainly I think from a standpoint of Raynaud's disease that that disease would cease to exist.

Not long ago I saw a patient who developed Raynaud's disease in this particular climate, some twenty-odd years ago. She moved to the Canal Zone and lived there for twenty-odd years and the Raynaud's disease ceased to exist; she came back to this country, to this section, not many months ago; the Raynaud's disease reappeared and she came into the clinic and Dr. Adson operated on her, and relieved that condition.

From the standpoint of our other peripheral vascular diseases, particularly thrombo-angiitis obliterans, it's quite obvious that patients would be much better off, and we would have fewer amputations, if the sympathetic innervation to the involved extremities, was completely interrupted. And as a matter of fact our statistics show, and of this Dr. Adson is well aware, that after sympathectomy for thrombo-angiitis obliterans our percentage of amputations is considerably less than that of the unoperated cases. There are many other phases of this subject which I would like to discuss but time does not permit.

DR. MANN: We have a few more minutes left before it is necessary to go to the other meeting. Who will very quickly keep on with this discussion, so that we will have no delay and these precious minutes will not be lost? If no one responds I am going to call on someone to continue the discussion. All right, Dr. Best, have you anything to say on the subject?

DR. C. H. BEST: I wouldn't like to let you down but I really haven't anything to say except that I was very much interested in Professor Cannon's remarks. It seems that almost every laboratory in the country is taking keen interest in hypertension. One shouldn't always refer to things going on in one's own laboratory but a portion of it comes to mind. Two of my colleagues have worked out a very convincing demonstration of the fact that some humoral substance does appear in these hypertensive animals, the Goldblatt hypertension, which can be transmitted to normal animals. Some evidence of this was, of course, brought forward by Housay and his collaborators and also by others. But by means of what we've called exchange transfusions, by a pump which will interchange at the rate of 20 or 30 liters an hour blood from one animal to the other, and yet not interfere with the blood volume of either, it's possible to show that this substance can be transferred from a hypertensive animal to a normal one and a very significant rise of pressure occurs in the unoperated animal. Instead of using the Goldblatt clamps, which of course are very efficient, it's equally satisfactory just to take out one kidney and put a plaster of Paris cast on the other, to prevent the compensatory hypertrophy, and tremendous hypertension, of course, develops very rapidly. Then when these dogs are joined, it's really just a transfusion of equal volumes both ways, the hypertensive effect becomes immediately apparent in the recipient.

DR. MANN: The surgical phase of our subject will be discussed by Dr. A. W. Adson.

DR. ADSON: I think we're very fortunate in having Dr. Cannon here today to give us his summary of his physiological experimentation on the autonomic nervous system, because it is apparent that there are a number of diseases that result from abnormal conditions of the sympathetic nervous system. And as a clinician and surgeon I've been very much interested in this problem for a number of years. All of you are familiar with the fact that Leriche suggested that by periarterial sympathectomy you might alter the vasomotor tone of the peripheral arteries. But as Dr. Cannon told you in his address, it is apparent that the nerve supply follows the artery for but a short distance, and that new fibers enter the sheath of the artery at corresponding levels, and this fact has led

to some of the more or less radical sympathectomies with the hope perhaps that we may alter the spasticity that does exist and is responsible for such diseases as Raynaud's and other allied peripheral vascular diseases where vasospasm plays a role.

Shortly after Royle advocated ramus section, I attempted to reproduce the same result in the hope of relieving spastic conditions. Instead we learned that an extensive lumbar sympathectomy, removing the trunks and dividing the rami, produced a vasomotor change apparently permanent; we then applied it to Raynaud's disease. This was done first in 1925, and that same person today is completely relieved of a Raynaud's disease affecting toes and feet and in the lower part of the legs. But when we began to attempt to treat the conditions of the hands, we met with some difficulty and some disappointments. Apparently the distribution to the arteries of the hands and fingers is somewhat more complicated than is the distribution of the lumbar group which supplies ultimately the vessels of the toes and feet.

At the present time, there's some argument as to whether or not we should divide the preganglionic rather than post-ganglionic fibers. I think I can state very definitely because we've had quite an extensive experience, and speak this fact—that from our own experience, it would appear that the thoroughness of the operation plays a much larger role than the mere question of pre- or post-ganglionic section. At the present time there are some operations that have been advocated which consist of dividing the trunk of the thoracic chain below the third thoracic sympathetic ganglion with an avulsion or division of the rami to the second and first. We have tried this operation and find that we have not obliterated all of the vasospasms. Therefore, in reviewing our own cases, it is apparent that if we can carry out a thorough interruption of all of the vasomotor fibers whether they're pre- or post-ganglionic to the hands, a permanent vasodilatation takes place, and we have many patients who have been very carefully studied before and after operation, years afterward, to substantiate this statement. So that this work in which Dr. Cannon has been a pioneer I am sure will contribute more and more as time goes on in the control of these various diseases.

Time does not suffice to take up a discussion of hypertension in which I've been very much interested and shall discuss tomorrow, except to say that my first stimulus came from the fact that when a spinal anesthetic was given to a patient for some abdominal or perineal operation, a drop in blood pressure always developed. And in the early history of spinal anesthesia this drop in pressure was a serious situation. As I watched these hypotensions, it occurred to me that if it would be possible to rob a vascular bed of sufficient size, of its central influence we might create a reservoir and reproduce the same changes that took place when you administered a spinal anesthetic. And naturally our first method was to do a laminectomy and divide the anterior roots from the sixth dorsal to the second lumbar inclusive on both sides.

That operation is a rather heroic procedure and has been altered. I shall be pleased to review tomorrow our experiences, our successes, our failures; but I want to emphasize one point whether you are attempting to treat Raynaud's disease or peripheral vascular disease or hypertension, the only ones that you can hope to alter are those patients who present a vasospastic phenomenon. And above all, select patients in whom there is some likelihood of securing the results you desire to accomplish.

CLINICAL PHYSIOLOGY OF THE GASTRO-INTESTINAL TRACT

Chairman: DR. OWEN H. WANGENSTEEN
Professor of Surgery
University of Minnesota

Leader: DR. ANTON J. CARLSON
Professor of Physiology
University of Chicago

DR. WANGENSTEEN: We are celebrating now the Fiftieth Anniversary of the establishment of this medical school. In that original group of teachers at this school the only full-time preceptor was the professor of chemistry, who in all likelihood was an adjunct from the department of chemistry. Whereas throughout the country, schools boasted men who professed an interest in physiology, there were very few departments of physiology. At the invitation of President Eliot of Harvard, Bowditch organized the first department of physiology in a medical school in this country in 1871.

In the last two decades there has been a general pyramiding of interest in functional studies. Yet, today, physiology in the ordinary curriculum does not have assigned it the number of hours which the importance of the field justifies. The apparent lack of interest on the part of the clinician in clinical physiology has probably been due in no small part to his inadequate orientation obtained in the subject while an undergraduate medical student. However, the interest of the clinician in physiology is being augmented daily by observations in the wards which show the great importance of physiology for the practice of medicine. Those who concern themselves with disturbances of the alimentary canal have the opportunity to observe daily the necessity of employing physiologic approaches to the solution of gastro-intestinal problems.

On the part of physiologists who term themselves general physiologists there have been many who have given the alimentary canal and its appendages their best thought. The leader of this discussion is, amongst that group, one of the keenest exponents of the physiology of the intestinal canal. It was in this Northwest Territory that William Beaumont, now somewhat more than a century ago, made one of the most important and original contributions to the understanding of digestion that has ever been made. Our speaker too has had his Alexis St. Martin and, together with his pupils, has contributed a great deal to a better understanding of the physiology of gastric secretion.

DR. ANTON J. CARLSON is at present Professor of Physiology and Chairman of that Department at the University of Chicago. Doctor Carlson was born in Sweden and came to America at the age of sixteen. He had his early training at Augustana College and after an interval began his scientific studies at Stanford University in California where he earned the Doctor of Philosophy degree. Aside from a brief interval in 1904 when he was engaged in research at the Carnegie Institute he has spent his whole scientific life at the University of Chicago, where he has had a profound influence on educational and research policies and where he has carried on his scientific work.

Doctor Carlson's studies have dealt mainly with the physiology of the digestive system and of the endocrine glands. He has studied the physiology of hunger and appetite and provided much important information about such disease states as gastric ulcer. He has had a great influence on American physiology through many students who have been trained under him and who now hold important positions in other American universities and research institutions. His students hold professorships in about twenty other American universities.

There are many clinical problems in the gastro-intestinal canal that will be more readily understood when gaps in our knowledge of the normal function of the alimentary canal are less numerous. What specific theme Dr. Carlson has chosen for this discussion, I do not know. The title affords him unusual latitude. Clinicians interested in gastro-intestinal disorders are happy that general physiologists of the stamp of Dr. Carlson interest themselves in these problems. Confronted with the enigmas of etiology and the baffling problems of therapeusis presented by such conditions as ulcer, appendicitis, constipation, bowel obstruction, and deficiency diseases having their origin in malfunctioning of the digestive tract, like the Apostle Paul, the clinicians cry out to the physiologists, "Come over into Macedonia and help us." It affords me great pleasure to present to you Dr. A. J. Carlson, Professor of Physiology at the University of Chicago, whom all of you know. Dr. Carlson will take over the reins of the discussion.

DR. CARLSON: The clinical physiology of the gastro-intestinal tract obviously can not be discussed adequately in an hour's time. The cardia, the pylorus, the stomach, intestinal peristalsis

and paralytic ileus, and the large bowel alone—any one of these could not be exhausted in such a discussion.

The logical man to open this discussion is Dr. Cannon of Harvard who did the earliest significant work on the gut with the x-ray. Dr. Cannon also was the first to establish the motility of the empty stomach in connection with hunger. I first became specially interested in the alimentary tract years ago partly because I had an "Alexis St. Martin," and some of the work on motility and secretion of the stomach in normal man was followed out, of course, on animals.

For the last five or six years my students and I have been interested in problems of the large bowel, so far confining these studies to the dog. In beginning this discussion I just don't know where to start. It remains to be seen if I know when to stop. The best way would be for the clinicians to take charge of the discussion entirely, while I listened. Perchance my experience might throw some light on the difficult scene. Many of these problems are still in the "No Man's Land."

Take the motility problem alone. We have now pretty well explored the action of the efferent extrinsic nerves of the gastro-intestinal tract. We have two types of nerve action: one producing increased motility or increased tone, the other producing inhibition, by direct action or by liberation of choline or of sympathin. This seems very uniform in man and the animals. But in the experimental animal the effect of loss of action of these nerves produces but slight and temporary effects. Section of the nerves may produce a temporary disturbance in motility of the stomach, but it is astonishing how quickly the stomach, pylorus, large and small intestine adjust themselves and carry on the work very well. One puzzle to me in regard to the large bowel is this: the removal of all extrinsic nervous control of the gut in animals like the dog produces far less disturbance of the large bowel than section or crushing of the spinal cord in the thoracic or lumbar region in man. Important as is the study of these nervous relationships to motility of the large intestine in the dog, cat, rabbit, rat, we shall undoubtedly find species variation in the capacity of adjustment. Those of you who are bald-headed and gray will recall the old days of gastro-enterology when our main problem was "dyspepsia" and the universal remedy was pepsin and hydrochloric acid. "Dyspepsia" has disappeared, I hope, even from the prairies of Minnesota and I don't know how many tons of pepsin and hydrochloric acid were administered while this theory was green. I can see very well how hydrochloric acid can be useful under certain circumstances but the astonishing thing to me has been the ability of the human gut to adjust itself with little or no gastric digestion going on, as is well known in the chronic case of achlorhydria, apparently from early childhood, if not from birth, and with fair intestinal digestion still taking place.

Then came the period of "autointoxication," the period of Metchnikof. I don't know what you think of autointoxication as the universal cause of human ills, but I am quite certain it is overdrawn. I can give you an instance in my own experience, discovered by accident. In the early days when yeast was supposed to be the "cure" of many gastro-intestinal ills, I was asked to make a study on the effects of yeast on alimentary function in man. I did it on some hundred medical students, men and women. One medical student, an ex Texas cowboy, proved to have on the average, one to one and a half bowel movements per week. He was a boy between twenty-three and twenty-four. When I saw his record I thought he must be either dying or half dead. He really did have only one and a half bowel movements per week but he was perfectly healthy, with no evidence of autointoxication. I am perfectly certain that if the other students had done something to suddenly delay their large bowel evacuation for four or five days they would have had all kinds of trouble, headache and malaise. If changes come on gradually, apparently there are capacities for adjustment to distension without disturbance and possibly even capacities for diminished absorption of toxic substance.

Now, so far as the extrinsic gastro-intestinal nerves are concerned, the local motor and secretory tissues carry on without them through chemical factors. It doesn't mean at all that when these nerves are present and active they cannot under certain conditions produce serious motor and secretory disturbances. In other words, the fact that the gut can carry on without the extrinsic nerves doesn't mean that these

nerves can be forgotten when the doctor is confronted by his patient.

A great many chemical factors have been assigned the role of motor control of the gut, particularly acetylcholine. I haven't yet seen any experiments that are conclusive enough to demonstrate to me that we have yet put our finger on a specific motor hormone of the gut as a whole. But we have a specific hormone aiding in the motor control of the gallbladder, and the depression of gastric motility by fats appears to be due to a hormone developed by the gastro-intestinal mucosa when acted on by these fats.

We have become rather interested in the cause of the partial to complete suppression of the gut motility in peritonitis. There are apparently reflex mechanisms, from the peritoneum through the central nervous system, to explain this paralysis of the gut on reflex grounds. I am inclined to think that, even with all the extrinsic gut nerves eliminated and central reflexes gone, motor paralysis of the gut by direct action or toxic bacterial products or acting by local reflexes in the gut, may still occur. Certainly bacterial toxins intravenously administered in the dog will cause total paralysis of the motility of the colon at least for twenty-four hours but we have not yet totally denervated the whole length of the gut.

I don't think the problems of secretion of bile, pancreatic juice or of gastric juice are of primary clinical significance except, possibly, with ulcers. It is remarkable, if other factors are right, how much one can suppress pancreatic secretions and gastric secretions without causing symptoms (at least in the experimental animal).

In the early years I was interested in the sensitivity of the gut in connection with the problems of pain, hunger, and thirst. There is no doubt that dull pain or even acute pain can be produced through naked nerve endings in the wall of the gut. These pain nerves may be activated either by muscular spasm or by distention, as by gas or fluid, yet one can have spasms without producing conscious pain both of the cardia and the pylorus. I haven't seen any evidence that the pyloric spasm of infants, sometimes called hypertrophic pyloric stenosis, is especially painful.

However, there is a still bigger problem on which I have not seen any way of getting on. The reason is that you can't do very much with it on the experimental animal. It is this: the change in the efferent stream of impulses from the gut that leads to the depression which we see where there is disturbance of the normal gastro-intestinal mucosa plus possibly some disturbance of motility. That disturbance of the general state of consciousness seems to me out of all proportion frequently to the extent of the mucosal lesions or degree of the disturbance of motility that we find. This is one of the large terra incognito in the pathological physiology of the gut.

I am afraid I don't take my own medicine. I really should have sat down and let the clinicians question me. I may have gathered some insight through years of labor. At least I have learned to observe my own gut. I think that early observations of Cannon on the cat still apply to dog and man. I know it applies to me. I was in the midst of the study on motility of the empty stomach in man, and attempted to demonstrate some of the new findings to members of the Physiological Congress in Holland. To be sure that my stomach was empty I begged off from dinner with Professor Hamburger the evening before. I knew we were not only to be dined but wined as well and I didn't know what condition my gut would be in the next morning. My stomach was empty and I thought everything was all right and when I got the balloon in, with physiologists standing around, all I demonstrated was a perfectly flat line on the kymograph with complete gastric inhibition. Pavlov remarked: "This is also a physiological demonstration," which was perfectly true.

Dr. Wangensteen, when a physiologist follows the rabbit and a gastro-enterologist follows the rabbit they invariably meet because the machinery in health also figures in disease. I have lately been concerned with a chapter in a projected book. The chapter is on the criteria of normalcy. Normalcy is not a line but it is a broad band and it is in that broad band where the physiologist and the gastro-enterologist who does something else than worship the follies of the best, will invariably meet.

DR. WANGENSTEEN: Dr. Walter Alvarez has been particularly interested in the influence of the autonomic nervous system upon the digestive tract. Dr. Carlson's remarks, I am cer-

tain, have stirred up in Dr. Alvarez some interesting experiences that he would like to comment upon now.

DR. ALVAREZ: As clinicians we are interested in the colon when it doesn't do its work, or when it does it too thoroughly and too vigorously. So often we hear that constipation should be divided into two great groups, those in which the colon is either atonic and those in which it is hyperactive and spastic. My feeling is that the colon would always be strong enough to do its work if the nervous system would only leave it alone. Many of you here must have had experiences which showed you that constipation is primarily a nervous disease. For instance, I know a woman whose bowels moved regularly twice a day until years ago she contracted an unhappy marriage. She immediately became severely constipated and started going from one physician to another. After many years of this she fell in love with another man, and with the coming of happiness she lost her constipation and the resultant indigestion and headache.

An old physician once told me about a rancher's wife who came a long distance over mountain roads to consult him in regard to severe constipation. Because static electricity was popular in that day, the doctor put an electrode into the woman's rectum and gave her twenty minutes of sparks. She wrote later that she was entirely cured and very happy. A few years later when she returned for another treatment, the doctor had lost interest in static electricity and his friction machine was not running. The woman, however, wouldn't be put off. The doctor tried his wall plate, but that too was dead. Then he found the metronome would still run so he connected her up and gave her twenty minutes of "tic tocks." To his astonishment she reported later that this had cured her, and then he knew that she had a psychic type of constipation.

I know that in my own case a bowel which is as regular as a clock when I am on a vacation can become constipated when I am under strain and fatigue from overwork. I can remember times when I became constipated suddenly because of worry over the illness of one of my children.

We all know that in many persons the colon is very sensitive to emotion. We have all seen patients who developed diarrhea when anxious or worried or frightened. Many of the diarrheas which I see are due at least partly to a congenital tendency to the emptying of the colon under excitement. This tendency is very marked in the apes and the monkeys. Whenever a physician cannot find a physical cause for diarrhea he should make certain that the patient isn't worrying over a lawsuit or an impending divorce.

One of my patients one day said, so wisely, "Doctor, if I could only be worried to the right degree my bowels would be perfect. If I worry a little they get constipated, and if I worry much they get loose." I have known many persons who have diarrhea all day when they are going to take a train in the evening. I have known many girls who couldn't go out with a beau without getting diarrhea or being much frightened for fear that they would get it.

You clinicians know that one of your greatest problems is that of the woman with a sensitive colon. I beg of you not to tell her that she has colitis simply because her roentgenograms show a spastically contracted descending colon with perhaps a little crinkliness on the edges due to spasm. There are two reasons why we shouldn't tell these people that they have colitis. One is that we all know they haven't a true colitis. If one opens the abdomen one finds a perfectly normal looking colon, and if one looks through a tube into the sigmoid loop one sees a normal mucosa. Furthermore, these people, even if they live into their eighties, never come to any bad end because of their sensitive colon and their excessive secretion of mucus.

The other tremendous objection to telling these women that they have colitis is that the victim will promptly ask her friends if anyone knows anything about colitis, and then if someone speaks up and says, "Why yes, my brother had chronic ulcerative colitis and he was dead in six months," the patient becomes scared to death, and then no amount of reassurance may ever straighten her out again.

I tell these patients that they have a highly sensitive colon which they inherited from their ancestors. They will have it all their days and they must learn to live with it. It will become

less sensitive as they grow older. I tell them it would be a perfectly good colon if only their nerves could leave it alone.

Today we realize that when autonomic nerves are stimulated, chemical substances, which have powerful effects on smooth muscle and glands, come out of the endings. Interestingly, when Dr. Chester Jones and one of his associates took some normal students and injected them with acetylcholine, the substance which is formed at parasympathetic nerve endings, he could see through a sigmoidoscope that the mucous membrane changed in appearance, and mucus and fluid came out of it. Interestingly also, one day when Dr. Jones called an artist to make a water color drawing of the appearance of the mucosa, the student happened to glance up, and when he saw a pretty girl looking into his rectum, he blushed violently all over the inside of his bowel!

I have long felt almost certain that such changes in the circulation of the bowel must take place under emotion, and they must account for some of the sudden attacks of flatulence and bloating which are suffered by nervous people. Years ago Sinelnikoff transplanted a segment of jejunum under the skin of the thorax, preparatory to making an artificial esophagus for a patient. He could see then that under the influence of emotion the mucosa changed from a dull pink to red. Similar changes were observed by Beaumont when he looked into the stomach of Alexis St. Martin.

Years ago the question occurred to me, Why is it that the colon is so much more reactive to emotion than is the rest of the digestive tract? Then as I thought a little more, I said to myself, "No, the esophagus at the other end is perhaps even more responsive to emotion." The other night I sat in the theater alongside of a man who suddenly, when the hero of the play got into an extremely dangerous and unpleasant situation, began to belch repeatedly and apparently painfully. He obviously was almost strangled by the waves which, because of his excitement, began to run back up his esophagus. How many of us physicians there are who have "the burps" and heartburn all afternoon simply because we took guests to the club for luncheon. We wouldn't have had any distress if we had eaten quietly by ourselves at home.

It seems to me that the reason why the two ends of the digestive tract are so reactive to emotion and nervous strain is that they are most influenced by the spread of impulses from the somatic nerves, which come close to the autonomic ones at the orifices of the body. Clinically, then, whenever we see a woman with a tale of woe about a sensitive colon that hurts and burns and won't empty itself right, let us first have great sympathy for her because her distress is very real. I know it is real, because my mother bequeathed me such a colon, and occasionally under heavy psychic strain I have suffered the same type of constant torture that these patients so often describe. When a woman tells you that she takes two or three enemas a day to try to get relief from a constant burning and consciousness of her rectum, don't sneer at her and don't get angry at her. I assure you that if you had the same distress you would soon be nearly frantic, and if you could get relief from frequent enemas, you would take them.

I beg of you also that when such a woman comes you do not tell her immediately that she has a redundant colon or a spastic colon or a long sigmoid loop or some other common and harmless anatomic variant that she can worry herself sick about. Usually I have to x-ray the colon of such a woman once or twice simply to help get rid of a fear which, with the best of intentions, someone implanted in her mind. Often she says, "But Dr. So-and So told me that I had a long sigmoid loop. What are we going to do about it?" And then sometimes I remind her that my cook is four feet ten and my son-in-law is six feet five. Are they diseased? No, neither of them is diseased; they are both very healthy, normal persons. They simply represent varieties of the human species. Similarly, the woman's colonic peculiarity does not represent disease and is not responsible for her many aches and pains or even for her constipation. As you know, colons come in all shapes and sizes, and you can find all these shapes and sizes in the big husky members of your football squad here at college.

Furthermore, I would suggest that you not try to treat a sensitive colon with medicated enemas and diets and attempts to change the bacterial flora. The best results that I have ever seen have been obtained by finding out what sort of strain the woman is under. Find out why she is

unhappy and worried, and then try to help her to live more sensibly, to get more rest, and to live with her sensitive bowel. Many of these women can be greatly helped in this way. Occasionally, when the colon is burning and "raising Cain" a quarter of a grain of codein will bring peace and comfort. I don't think it is dangerous to prescribe this drug for sensible persons who will use it only occasionally. In thirty years I have never seen a habit produced by codein. I don't like the present day common practice of filling these poor people with phenobarbital. Sometimes it helps a great deal, but then it should be used intermittently and only on "bad days."

DR. WANGENSTEEN: Method is as important as an idea in the solution of a problem. There are many who have had an excellent idea who have failed in their objective because of want of a proper approach or technic with which to attack their problem. When a man with good, original ideas possesses as well, mastery of technical methods, worthwhile contributions follow as a matter of course. Dr. George H. Whipple, who is in the audience, made an abiding contribution to the knowledge of intestinal obstruction when he devised the "closed-loop" method of studying the effects of obstruction. I am wondering whether Dr. Whipple will not, on this occasion, say something of his first scientific love—intestinal obstruction.

DR. WHIPPLE: I came here today to listen and have enjoyed the discussion very much, and particularly this opportunity of chatting with my old friend, Dr. Alvarez. It is so long since I worked with the subject of bowel obstruction that I should prefer to remain one of the audience.

DR. CARLSON: I, of course, followed Whipple's pioneering work and some work was done in my laboratory upon the machinery inducing the symptoms of bowel obstruction. The problem is not completely solved yet, but I ought to add a little to what Dr. Alvarez said. There is no doubt that those conditions he described are in the main correct. I can verify some of them on my own person. But here is the puzzle that there are any number of people, men and women, who are under equal or greater strain and they don't show gut disturbances. Where is the differential?

DR. ALVAREZ: May I mention you said once that you hoped that day might come when you could cut your systemic nerves and go about your work in peace and quiet?

DR. CARLSON: The trouble is I delayed too long; now we know perfectly well we would have to cut the whole mess.

DR. WANGENSTEEN: As most of you know, Dr. Edward A. Boyden of the department of anatomy in this school has been very much interested in the mode of origin and transmission of painful stimuli having their origin in the intestine. Dr. Carlson's discussion of visceral pain has undoubtedly brought to Dr. Boyden's mind some things upon which he would like to comment.

DR. BOYDEN: Visceral pain is a large subject and one that I would not venture to discuss in this short time. But while listening to Dr. Carlson and Dr. Alvarez I have been impressed by the attention given to the action of extrinsic nerves upon the colon. I should like to ask Dr. Carlson to discuss the reverse effects—what is known about the action of nerves from the colon upon the rest of the body, as, for example, the effect of distention of the colon upon the secretion of bile. Perhaps, also, he would tell us something about the hormones secreted by the large intestine?

DR. CARLSON: There is no difficulty of showing, of course, that distention of the colon through stimulation of sensory nerves in the colon will induce many kinds of reflexes. So far, we have done it only on experimental animals. I did some of it years ago when I started this work on visceral sensibility. But in any individual human patient, it is going to be dfficult to say whether the gas, distention, or spasm is the cause of pain that leads to disturbance in the body. Of course, these are "hormone days" and I have, I think, unfortunately assumed some, or labeled some in connection with the gut, prematurely, in past years. I don't know whether we have real hormones from the large bowel or not; it is going to be very difficult to prove or disprove it, in my judgment. Certainly by the exclusion method, by the removal of the entire large bowel, no defects are produced that have so far been detected, mainly because it is just

one factory of the hormones and some are produced somewhere else. In other words, the method of extirpation, which works in the case of parathyroids, anterior pituitary, etc., is of little value here. Concerning hormones which govern gut motility in health and in disease, it seems to me that on that subject we are where we were forty years ago when we started to study the effects of intravenous injection of crude tissue extracts on the blood pressure. This was before the discovery of adrenalin and of pituitrin. Many actions may be induced by parenteral administration of crude extracts, in acute experiments. But it is another story to prove that the substances responsible for such actions in acute and crude experiments are also produced in the body as part of the machinery of health and of disease. Have I been sufficiently vague, Dr. Boyden? In that case, come again.

DR. LEO G. RIGLER: For many years we have heard roentgenologists discuss the observations of Forssell anent the independent movements of the mucous membrane of the digestive tract, but physiologists appear to have given his theories scant attention. Forssell believes that the mucous membrane of the stomach moves freely and without reference to the remaining segments of the gastric wall. Furthermore, he believes this results in the formation of small, independent digestion chambers. I should like to hear Dr. Carlson's comments on the validity and importance of these theories.

DR. CARLSON: I am quite familiar with the apparently independent motility of the intestinal villi, following the work of my pupil, Dr. King, now at Vanderbilt. In some species these villi are not present in the intestinal mucosa. When present, they seem to move quite independently of the neuromuscular machinery of peristalsis. Certainly the villi are absent from the stomach. Mucosal motility in the stomach must be governed by the muscularis mucosa, because there is no other machinery. There is nothing to suggest the gastric mucosa has ameboid power. But anybody who has studied the swaying and pumping action of the intestinal villi will realize that where present the villi are a physiological mechanism of the first order.

DR. JAMES B. CAREY: The explanation of gastric pain with respect to the lesion involved has always interested me, particularly since I have been doing gastroscopic work. It isn't hard for me to explain, very crudely perhaps, the occurrence of gastric pain, given a deep indurated ulcer involving all of the layers of the stomach; but when I visualize with the gastroscope what seem to be insignificant punctate submucous erosions or a condition of atrophy of the mucosa or single submucosal hemorrhages, it is difficult to reconcile the complaint with the lesion. Some of these people complain quite bitterly of pain, comparable to that of an ulcer; on the other hand, individuals with objectively extensive lesions have no pain at all.

Dr. Schindler has mentioned numerous times that he has noted the occurrence of pain of severity equal to that of ulcer, the only explanation he could find being one or more submucosal hemorrhages in the stomach. I can't imagine such a condition enduring more than a few days. On the other hand, one of the most extensive hemorrhagic ulcerative gastritis patients that I ever saw (probably secondary to a cirrhosis of the liver), involving the upper third of the stomach, observed gastroscopically on three different occasions, each time presenting the same hemorrhagic eroded condition, was accompanied by no symptoms referable to the stomach at all.

Certainly the relation between the visible changes in the mucosa and submucosa and the symptomatology puzzles me very much. For that reason it has been so very difficult to arrange a symptomatological picture for gastritis.

DR. CARLSON: Well, I don't know either but maybe in the future some of these puzzles which I have been seeing and hearing about during thirty years of attention to the problem will clear up by better experiments and clearer thinking. The great individuality and chameleon-like character of the gut is obvious. Early I ran up against this fact. In some perfectly healthy individuals powerful contractions of the stomach, the hunger contractions, produce no sensations. On the other hand, in other individuals, more or less nervous, the same degree of gastric contractions will call forth agony and cold sweat.

DR. WANGENSTEEN: The hour is growing late, I know, but before we adjourn there is one question I should like to ask Dr. Hal Downey of the department of anatomy in order that we

may have his reaction as well as that of Dr. Carlson.

It is my impression, Dr. Downey, that there are problems in gastro-intestinal functional studies that may be attacked most effectually through a joint approach of microscopic morphologist (histologist) and physiologist. We all know of the corroboration lent the functional studies upon the secretion of isolated gastric pouches (Heidenhain) by the splendid morphologic studies of Bensley. Could not the morphologist, working in intimate collaboration with the physiologist, give us helpful information concerning other physiologic processes?

DR. DOWNEY: I think it would be possible to carry on experiments on the physiology of the digestive tract from different standpoints, that is, coöperative research in the best sense of the word.

Many problems which seem to be primarily of interest to the surgeon, some of which Dr. Wangensteen has been considering recently, depend on the fields of physiology, histology, pathology, and even hematology for their final solution. One can think of many problems in the physiology of the digestive tract which require the coöperation of men working in these different fields.

DR. CARLSON: I agree with Dr. Downey, but the use of the microscope, alone, on the gut has reached a sort of impasse, unless combined with other technics. A budding medical investigator said, forty years ago, that at that time everything that could be discovered by the microscope had been discovered. That is not so, even today. Histologists can surely help, but the days when the clinical pathologists can use the microscope on dead tissue alone, and help us forward, that day, I think, has passed. What does the physician do, who attempts to answer nature's questions now? He does physiology, even on his patients. What does the anatomist or the pathologist do? The pathologist is working mainly, not on the structure of dead tissue, but on pathological processes, and so in the entire field. What do the pediatricians, the gynecologists do? They are dealing with functions, with processes! That is one of the reasons why I have not lost much sleep over the fact that physiology is not given a greater amount of attention in the medical curriculum. Now, all doctors become physiologists, some good ones, others not so good. With reference to the way we do it at Chicago, we give the students some free time to think or to waste, then if there is a physiologist, like Luckhardt, who really has something to teach these medical students, these students have pretty good noses and they find it, and as a result in Chicago a large per cent of medical students elect advanced work in physiology, sometimes up to 50, 60, or even 70 per cent above the so-called prescribed medical course. I think that is best. When the students have an opportunity to select what they want, they are not driven. Moreover, I think the teacher, under these conditions, is a little more on his or her toes. I don't object at all. Medical education is in some places so regimented that the student has little or no time for elective work, no time to find himself in the particular field where his love is directed at present, where ultimately his life work is going to be done. I think the answer lies in more freedom for election because, somehow, the kind of men and women that now get into the medical school are mostly far beyond the idea of getting snap courses. They really are after the facts.

DR. WANGENSTEEN: I am certain, Dr. Carlson, that I bespeak the genuine sentiment of this group when I say that we are grateful to you for this very interesting round-table discussion relating to the clinical physiology of the gastro-intestinal canal.

NEUROPHYSIOLOGY*

Chairman: DR. J. CHARNLEY McKINLEY

Professor of Nervous and Mental Diseases
University of Minnesota

Leaders: DR. DETLEV W. BRONK
Professor and Director, Institute of Neurology
University of Pennsylvania

DR. HERBERT S. GASSER
Director, Rockefeller Institute for Medical Research

Drs. Bronk and Gasser opened the round table with a general discussion of the pedagogical and practical relationships of neurophysiology to general medicine, neurology and psychiatry, covering the following principal points:

The minor position which neurophysiology has held seems unjustified when one considers, for example, the diagnostic importance of pain and a rising temperature in general medicine, both of which are fundamentally neurological mechanisms which still need much clarification. A tendency exists among many of our colleagues to think of neurophysiology as an abstract laboratory science which has not contributed to the solution of practical medical problems in proportion to the effort and expense which are necessary for its prosecution. But the fact is a commonplace that medical science advances so rapidly that the members of the profession must continually labor and strain in order that their concepts may not become obsolete. Pedagogically, therefore, the teaching of basic physiologic mechanisms in neurophysiology provides the student with the knowledge which enables him to adapt with facility to new revisions in clinical neurologic and psychiatric practice.

Advances in the practical field are most likely to arise from the broadening of our base through the elucidation of all available facts such as the functioning of the synapse and the perikaryon. As these points become more understandable they can be applied more and more to nervous system integration and, it is hoped, finally to the total behavior of the individual. It is not too farfetched, therefore, to think that the study of isolated neural phenomena may provide explanations which can be carried over into the solution of many of the mechanisms not only of organic neurology but also of civilization's most devastating group of illnesses, namely, the mental disorders.

*Reported by the chairman, Dr. J. Charnley McKinley.

DR. D. W. BRONK is Professor of Biophysics and Director of the Johnson Foundation for Medical Physics at the University of Pennsylvania. In his laboratory the brains and skill of electrical engineers and physicists are put to work to explore the physics of the human machine.

Professor Bronk's rise to leadership in a new type of Medical Research has been rapid (he is only forty-two years old) and his path is of interest. In the early 1920s he was a young scientist doing brilliant studies in the field of astrophysics. He became convinced that the viewpoint and many of the methods of the professional physicist could be applied to biological and medical problems and set himself to learn biology and especially physiology. Studies at Michigan, Swarthmore, Cambridge University and London quickly showed his ability in his new field and in 1929 he was selected to head the project for a biophysical institute in Philadelphia.

DR. HERBERT S. GASSER is at present Director of the Rockefeller Institute for Medical Research in New York City. He is a graduate of the Medical School of Johns Hopkins University and has been Professor of Pharmacology in Washington University in St. Louis, Missouri and Professor of Physiology at Cornell University, School of Medicine, in New York. He served as pharmacologist in the Chemical Warfare Service in 1918. He is a member of the National Academy of Sciences, the American Philosophical Society and numerous other scientific societies in this country and abroad.

Some recent dividends of this general approach are already in evidence; for instance, the use of liver in combined sclerosis, vitamin B_1 in neuritis, and potassium in familial periodic paralysis. The relationships of increased metabolic activity (hyperthyroidism) to nervous hyperexcitability has long been known and the indications for therapy reasonably well outlined.

Discussion

Dr. Starke R. Hathaway asked for an opinion as to the outcome of the problem of inhibition; whether this will be in terms of the general laws of peripheral conduction as we now know them, or whether new discoveries will be needed in the sense of an inhibitory type of neuron discharge or an inhibitory substance.

Drs. Bronk and Gasser both felt that, though

opinion should necessarily be rather guarded, the solution will probably be in accord with laws of the nervous system as now being discovered and elaborated, and that new laws or new functional systems need not at present be invoked.

Dr. A. B. Baker raised the point that frequently the neuropathologist can determine no histological alterations in cell groups in the brain which before death gave obvious clinical evidence of being damaged. He wondered if others felt as he did that the limitations of the microscopic technic were not the determining factor in such paradoxical situations and what suggestions could be reasonably entertained for shedding more light on such a dilemma.

Dr. Bronk said he had also been troubled by that problem. In his opinion, contributions from related fields (chemistry, electrophysics, for example) might ultimately clear up many phases of the problem.

THE MECHANISMS AND MANIFESTATIONS OF THE IMMUNE RESPONSE

Chairman: DR. A. T. HENRICI
Professor of Bacteriology
University of Minnesota

Leader: DR. MICHAEL HEIDELBERGER
Professor of Biochemistry
Columbia University

DR. MICHAEL HEIDELBERGER is associate professor of biochemistry at Columbia University and chemist in charge of the Mount Sinai Hospital Laboratories. He is widely known for his work on the chemistry of bacterial toxins and of immune reactions. His discovery that complex sugars found in bacterial organisms are of specific importance in immune reactions has been of the highest importance and has attracted worldwide attention. Professor Heidelberger holds the Ehrlich medal for his work in immunology.

Dr. Henrici opened the discussion by relating some experiments which indicate that following extreme infections with ringworm fungi in rabbits there can be demonstrated two sorts of hypersensitivity. When polysaccharide is injected, there develops a diffuse redness and desquamation of the skin. When protein is injected, there develops a circumscribed area of purpura, followed by necrosis and ulceration. Dr. Henrici asked Dr. Heidelberger if he had any other evidence regarding specific differences in the reactions of animals to different fractions of microorganisms. Dr. Heidelberger replied that he had isolated two specific polysaccharides from tubercle bacilli, which gave skin reactions in sensitized animals, as well as several other polysaccharides which were inactive. He stated that polysaccharides extracted from tubercle bacilli in earlier experiments had been drastically handled and were probably therefore inactive. One polysaccharide fraction was degraded by treatment with alkali, which splits off magnesium palmitate. The polysaccharide gives in tuberculous patients either an immediate wheal, or an area of redness which begins to develop in six hours and persists for 24 to 48 hours. This polysaccharide was considered to contain a residue protein. All traces of this protein were finally removed by treating the carbohydrate fraction with trypsin, which destroyed the antigenic property of the protein, and then destroying the trypsin by treatment with alkali. After this treatment, the polysaccharide no longer gave late reactions, but only an immediate wheal, or redness beginning 6 to 8 hours after injection and lasting only a few hours. Dr. Cournand found that the immediate wheal reaction was nonspecific, but that the 6 to 8 hour reaction was highly specific.

Dr. W. P. Larson asked Dr. Heidelberger's opinion regarding the relationship between the size of the globulin molecules and the efficiency of immune serum. Dr. Larson pointed out that in rabbit serum the globulin molecules are considerably smaller than in horse serum, and that rabbits produce more potent antipneumonia serum than do horses. Dr. Heidelberger agreed that there was a definite correlation, but stated that he could not explain the greater efficiency of rabbit serum unless on the basis that the small molecules could diffuse more readily into inflamed tissues than could larger molecules, and that weight for weight, rabbit antibody will combine with more pneumococcus polysaccharide than will horse antibody. Dr. Larson suggested that this might be due to the larger surface exhibited by the smaller molecules of the rabbit antibody.

Dr. C. H. Bailey discussed observations concerning an antigen extracted from tubercle bacilli, which was an ester of one of the inositols. Dr. Heidelberger stated he had not worked with lipid soluble fractions of the tubercle bacillus, but had confined his work to the protein and carbohydrate fractions of defatted cells. Dr. Bailey said he was impressed by the simplicity of the inositol molecule, and Dr. Heidelberger replied that this substance is antigenic only in the complement-fixation reaction, and is not concerned in the agglutination or precipitation reactions. Complement fixation is a more sensitive reaction, and antigens composed of small molecules may work in such a sensitive reaction.

Dr. C. P. Fitch asked Dr. Heidelberger if he had worked with human or bovine type tubercle bacilli, and regarding the nature of the medium upon which they had been cultivated. Dr. Heidelberger stated that he had used human, bovine and avian types of tubercle bacilli, and timothy grass bacilli, all grown on Long's synthetic medium. He could not demostrate any certain difference in the antigenic properties of the proteins in the human and bovine types. There are, however, definite differences between the protein fractions of human and avian type bacilli. He is working with rabbit serums, and with two horse serums. Dr. Fitch stated that avian type tuberculosis occurs in horses, and it might be possible to use serums from infected animals.

Dr. R. V. Ellis asked if it would be possible to read the tuberculin reaction earlier than is now the case if we used Dr. Heidelberger's polysaccharide fraction. Dr. Heidelberger stated that not enough clinical material had as yet been studied, but that it would probably be possible to read the reaction in 6 to 8 hours.

Dr. L. F. Richdorf asked Dr. Heidelberger concerning the relative merits of old tuberculin and the fractions which he is studying. Dr. Heidelberger replied that testing with old tuberculin was quite different from testing with definite fractions. In old tuberculin the antigens are partially degraded, and the polysaccharide in crude tuberculin is much less active than in the purified material. He pointed out that Dr. Seibert had found it possible to sensitize animals with carefully prepared unheated tuberculin, whereas this cannot be done with Koch's old tuberculin.

Dr. H. O. Halvorson discussed the mechanism by which antibodies are produced, and asked Dr. Heidelberger if the following statement accurately restated what Dr. Heidelberger had said in his morning lecture regarding this mechanism: The antigen affects the enzyme which produces globulin, and leaves its imprint upon this enzyme so that when new globulin is formed, it has impressed upon it a mirror image of the hapten groups of the antigen. Dr. Heidelberger stated that this was essentially correct, except that Dr. Halvorson had stressed the enzymes more than Dr. Heidelberger was willing to, and that the term "mirror image" was perhaps too definite. Dr. Halvorson asked Dr. Heidelberger to explain the tremendous increase in antibody after the second and third injection. Dr. Heidelberger stated that it was difficult to picture the exact mechanisms, but if antibody has already been formed, any antigen introduced is removed and transported more quickly and efficiently to the cells that form globulin. He pointed out that particulate antigens are better than soluble ones. Dr. Halvorson asked why all the antibodies should appear in the globulin fraction, and none in the albumin. Dr. Heidelberger replied by referring to the work of Dr. Florence Sabin, who suggested that globulins are secreted as a surface film from the cells of the reticulo-endothelial system in the liver, spleen and lymph nodes. Antigen introduced into the blood stream is phagocyted by these cells. This has been shown by the introduction of dye-antigen, in which case the colored antigen can be seen in the reticulo-endothelial cells. These cells apparently first split the dye from the protein molecule. It appears possible that the antigen molecules then affect subsequent globulin production in these cells.

Dr. Ellis asked if dye antigen localizes at all in the skin, and Dr. Heidelberger stated that it does not, unless it has been injected into the skin. Dr. Henrici pointed out that there is some evidence that in trichophytosis there occurs an actual sensitization of the epithelial cells, and that possibly one should not therefore generalize regarding the reticulo-endothelial cells being the site of all antibody reactions. Dr. Heidelberger replied that it would be highly desirable to study intracellular antibodies but that this is technically a difficult problem. The relative distribution of antibodies in the tissue juices and in the blood stream would be interesting. He has found that

rabbits may contain as much as 6 to 9 milligrams of antibody nitrogen per c.c. of serum, indicating that from ⅔ to ¾ of the total globulin may actually be antibody in extreme cases.

Dr. Heidelberger asked Dr. R. A. Gortner his opinion regarding the role of salts in immunity reactions, whether he still believes that agglutination and precipitation occur in two phases—a preliminary combination of the antigen and antibody, followed by a precipitation due to the effect of an electrolyte on colloids. Dr. Gortner replied that this was still his opinion, and asked what other mechanism could be proposed to explain the actual flocculation. Dr. Heidelberger admitted that the antigen and antibody are combined in the absence of salts, but believed that there was another explanation for the influence of salt upon flocculation. He believes that agglutination and precipitation reactions represent a mutual interaction of multivalent compounds, namely the antigen and the antibodies. These combine to form large aggregates. In the absence of electrolytes, this reaction is limited by the accumulation of Coulomb forces due to the many ionized groupings on the forming aggregate. The presence of salt provides an ionic atmosphere which abolishes these forces and tends to allow the formation of large aggregates.

Dr. Gortner replied that such a phenomenon is essentially a coacervation between the antigen and the antibody, separating a liquid phase. Dr. Heidelberger replied that he considers the agglutination to be a purely chemical reaction from start to finish, and that the reduction of surface potential is merely a by-phenomenon. To support this he related an experiment in which type I pneumococci were added to excess of specific serum. The organisms were agglutinated as very fine aggregates which did not settle. The bacteria were then centrifuged and washed with salt solution until no antibody could be detected in the supernatant fluid. They were then resuspended in salt solution, and the suspension was divided into two parts. One part was allowed to stand, and the organisms were found to remain in suspension. To the second part, more type I pneumococci were added, and it was now found that complete agglutination took place. Dr. Heidelberger believes that with an excess of antibody the chemical reaction is interrupted in an early stage. If now we add an excess of bacteria, the new bacteria become linked to free side chains on the previously treated bacteria, and large aggregates are formed. It was found that if to the previously treated type I pneumococci one adds a nonspecific antigen, that is, type II pneumococci, no agglutination takes place. Dr. Heidelberger believes that this indicates that the reaction is a chemical one.

Dr. Gortner admitted that the phenomenon of *specificity* was the primary stumbling block to a purely colloid-chemical interpretation of the antigen-antibody reactions since colloid chemical reactions are ordinarily not highly specific, depending as they do purely upon surface forces. On the other hand, he insisted that one could not wholly ignore colloid surface behavior in immunity reaction, since to do so would be to set such reactions apart as a wholly separate class and to assume that the colloidal systems which are present no longer show the characteristic behavior which such systems should exhibit. The proper interpretation and the greatest chance for advancement of knowledge, in his opinion, lies somewhere in the middle ground between (1) specific chemical (or physical) reactions which are determined wholly by the nature and probably as well by the location in space, (on the surface) of reacting groups (e.g. $-NH_2$, -COOH, etc. etc.) and thus bring about specific and induced space orientation of the reacting micelles; and (2) the physico-chemical behavior characteristic of lyophilic colloid systems in general. Since electrolytes do profoundly affect the electrokinetic potential and lyophilic colloid hydration in the most diverse types of systems, they must contribute something to the net result of agglomeration and flocculation in the phenomenon of agglutination of bacteria. The big problem to which colloid chemistry cannot as yet contribute the answer is that of *specificity*. To answer that problem we will have to use all the tools and ingenuity we possess!